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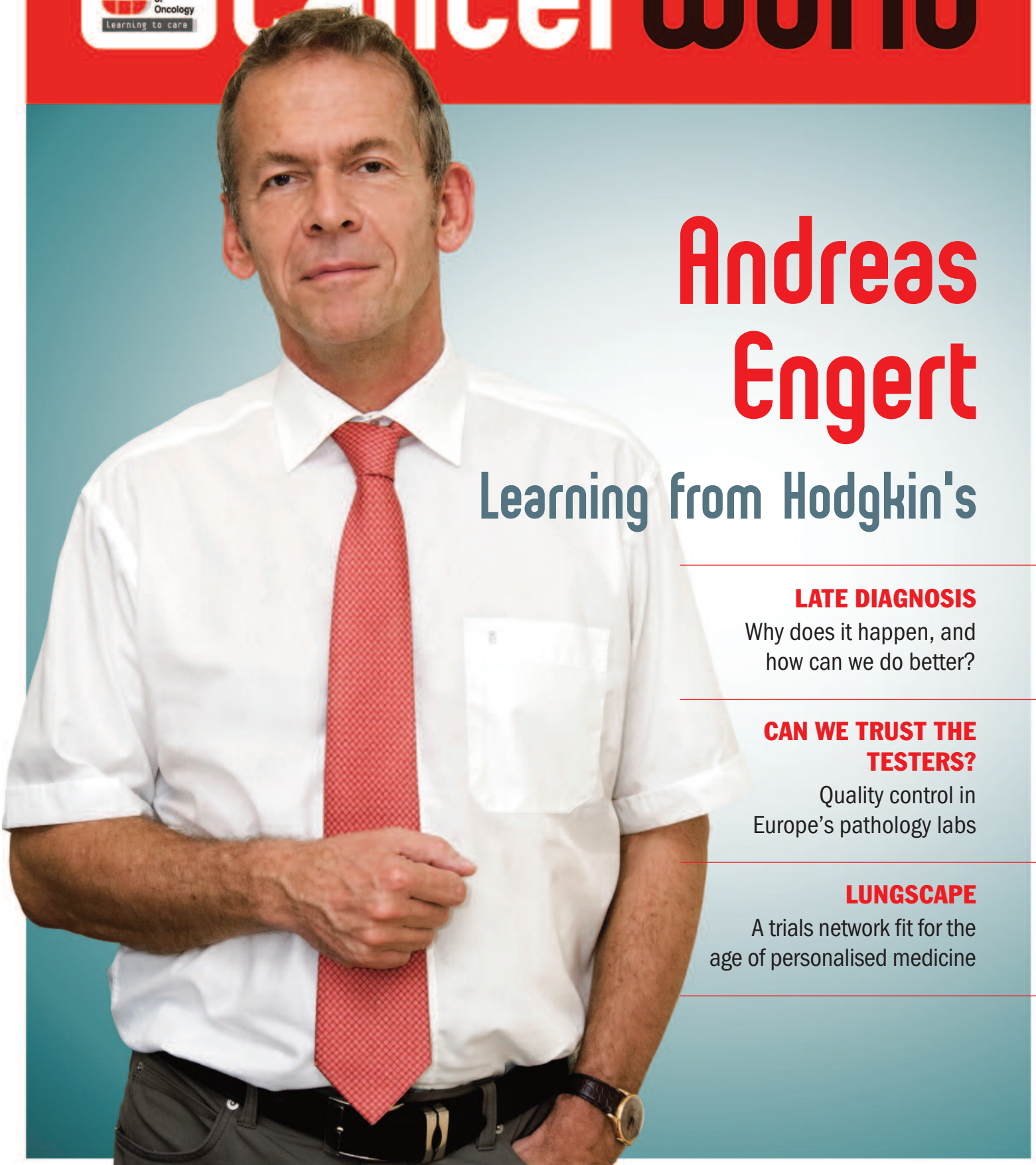

Andreas Engert

Learning from Hodgkin's

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Penalised for having cancer

KATHY REDMOND EDITOR

Much attention is given to the spiralling cost of treating cancer, yet the financial cost to survivors is rarely given any consideration. A recent Dutch study published in the *European Journal of Cancer* (vol 48, pp 2037–42) throws some light on the problem. Nearly a third of survivors experienced a change in their work situation as a result of their cancer. Some chose to give up work, others were unable to work because of their disease or had to switch to part-time work. A few were sacked. People also faced problems obtaining health and life insurance as well as mortgages. While many survivors did finally manage to obtain loans and insurance, they had to pay a higher premium or interest rate. This study mirrors findings from other countries, which have shown that having cancer often leads to a loss of income and/or increased expenditure.

In some countries patients have to bear the costs, either fully or partially, of their medication, tests, procedures and physician visits. But there are also many hidden costs. People can find themselves out of pocket because of higher utility bills, the need to buy new clothes because of weight changes, and the cost of special diets, wigs and prostheses. Travelling to a treatment centre can be very expensive, especially for those who live a long way away, and family members may also be hit financially if they need to accompany the patient, or stay close by while the patient is hospitalised.

As many cancers are becoming chronic conditions, these financial burdens can persist in the long term, and can be highly stressful for patients and their families at a time when they are already struggling to cope with the disease. Finding solutions won't be easy given the current economic climate in Europe, with rising unemployment, cuts in welfare benefits, and recent increases in living expenses.

Greater awareness of the social and economic burden of cancer could help ensure that patients are routinely asked about how they are coping financially, and are given advice about their rights and entitlements. The patient survey recently launched by the European Cancer Leagues, to build a better picture of social and economic problems, could be a very helpful contribution. Policy initiatives aimed at reducing the financial burden of cancer are also needed. These should include protecting employment rights and removing obstacles to accessing welfare benefits when needed. A number of organisations across Europe are currently addressing this issue, but these efforts are sporadic and not delivering for all cancer patients. It makes sense to join forces at an EU level to raise awareness about the financial consequences of cancer and to advocate for changes that could make all the difference to patients' lives. ■

Andreas Engert: Learning from Hodgkin's

SIMON CROMPTON

Hodgkin's patients survive for longer – but with more serious and lasting damage – than almost any other group of cancer patients. Finding ways to address the problems of both current and future survivors can provide valuable lessons for other cancers, argues Andreas Engert.

Why should we bother with Hodgkin lymphoma? It accounts for only 1% of cancers, and the probability of cure has improved dramatically over the past 40 years, with 94% of patients now expected to survive. Does it really deserve research funds and the attention of the wider cancer community?

The answer from the Hodgkin's research community is an emphatic yes. In the 1970s Hodgkin's became one of the first curable diseases in oncology, and ever since there have been important debates about best treatment and long-term risk/benefit balance that have real relevance to the wider world of cancer.

Hodgkin lymphoma, which most commonly affects young adults, focuses minds on patients' lives: how to give them decades of life free not only from the effects of cancer, but also from the effects of treatments used to cure them. These issues can only become of wider importance as more and more of the global population experiences cancer as a long-term condition. In the words of a recent editorial by Joseph M Connors in the *New England Journal of Medicine*, Hodgkin's is "The Great Teacher".

A leader in the quest for more acceptable, less toxic, approaches to treating Hodgkin lymphoma is Andreas Engert, chairman of the German Hodgkin Study Group (GHSG) and professor of internal medicine, haematology and oncology at the University Hospital of Cologne. He knows only too well that the problem with Hodgkin's is not so much how to cure it, but how not to kill with the

treatments. Engert was only 14 when his father was diagnosed with Hodgkin lymphoma. He was cured with chemotherapy, but then died 16 years later – when Engert had already embarked on his career in oncology – from cardiovascular problems resulting from treatment.

Such outcomes are not uncommon. Studies indicate that the risk of developing neoplasms after treatment for Hodgkin's is 22% at 25 years – an 18-fold increased risk compared to the rest of the population. People who have survived Hodgkin lymphoma also have a significantly increased risk of coronary artery disease, valve disease, congestive heart failure, pericardial disease, stroke, arrhythmia and sudden cardiac death.

JORGE NOGUEIRA

Since his father's death, Engert's career has been defined by searching for alternatives to current chemotherapy and radiotherapy regimens. It has been a quest that has seen him following and then taking up the mantle from Volker Diehl – the man who treated his father and one of the European giants in Hodgkin's research – and then firmly establishing his centre as a world leader in developing and evaluating new approaches for haematological and solid cancers.

In the process, Engert has sometimes found himself cast as a young radical, determined not to be bound by history, restless to move the agenda forward, and sometimes in profound disagreement with many in the Hodgkin's community about the right balance between effectiveness and toxicity in treatments.

But today Engert, now assistant director of the Department of Internal Medicine at the University Hospital of Cologne, believes that the

"They said antibodies are fine for distinguishing between tumour types. But treatment? No way"

long search for less lethal cures may have reached a vital juncture. The days of tortuous debate about which chemotherapy regimens are best may be numbered.

Engert is keen to talk about a new targeted drug – brentuximab vedotin, codenamed SGN-35 – which he says may be about to change everything in Hodgkin lymphoma. Results from trials in the US presented at ASCO last year showed that the drug induced remission in 75% of patients with relapsed or refractory Hodgkin's, with 35% achieving long-lasting and complete remission.

What is more, because it is an antibody-drug-conjugate – a combination of an antibody and a drug guided safely to its target – the dangers of systemic treatment and radiotherapy are avoided. The drug was registered in the US last year, and is expected to be registered in Europe soon.

"This is the single most effective drug we now have for Hodgkin's," says Engert, whose German group has successfully trialled the drug in refractory or relapsed disease. "It's thrilling for me – and I'm not just saying this because we get money from the pharmaceutical company to conduct clinical trials. It's thrilling because I worked on linking antibodies with plant toxins in the late 1980s when I was at the Imperial Cancer Research Fund. Trials eventually showed that these immunotoxins were not good enough because they were immunogenic [produced an immune response]. But now, 20 years later, this company has produced a very well-tolerated combination. So that story, for me, has now come full circle."

The story has come full circle in more ways than one. Six years ago, Volker Diehl – who led the development of the BEACOPP chemotherapy regimen for advanced Hodgkin lymphoma – described the regimen as a "great poison" in an interview with *Cancer World*. "I would like to have something better," said Diehl, who had spent decades working on improvements to chemotherapy. "Sometimes I wake up in the night and ask what will happen to my young patients in 10 to 15 years."

Now Engert, who was co-ordinating editor of the Cochrane Haematological Malignancies Group for 10 years, believes that "something better" may have arrived. What is more, after 30 years when monoclonal antibodies were being developed for other cancers, but there were no new drugs for Hodgkin's, several new targeted drugs for the disease are now in trials.

"The drug companies are now knocking on our door," says Engert. "Before, they always said it was too small a market – that since you cure most of these patients anyway, there's no use looking at the 10–20% who are not cured. They wanted to invest their money in other areas such as lung cancer. We had discussions for many years, with many drug companies. I remember in the 1990s we found a bispecific molecule that was pretty effective and Schering was interested in it, but the guys who had the money did the calculations and said no.

"It has been frustrating, given progress on new targeted drugs for other cancers. My interest has always been on antibodies, since I was a medical student. I remember that when rituximab first came out for non-Hodgkin lymphoma, nobody was interested. They said antibodies are fine for diagnostics, for distinguishing between different tumour types. But treatment? No way. We were one of the first European centres to take rituximab and use it in combination with chemotherapy, and for diseases like chronic neutrophilic leukaemia."

Born 1959 in Braunschweig, Germany, Engert rebelled against his father's wishes that he should become a banker, and decided to study medicine. When he was a medical student, his father kept urging him to go and see Volker Diehl in Hanover, the man who had cured his Hodgkin's with chemotherapy. "I said no," says Engert, with a smile. "Whatever you say, I do exactly the opposite – that's what many young men do I guess." As a medical student, he had initially focused on psychiatry and psycho-

JORGE NOGUEIRA

somatics, then decided it wasn't for him. He knew he didn't want to go into surgery, and he also knew that it was internal medicine – immunology, nephrology and oncology – that he found most interesting. So he changed his mind about Diehl.

"I realised that he was a really interesting doctor. I worked for him, wrote my thesis with him, and then followed him. My father and Volker Diehl were certainly very influential on the direction I took." Indeed Diehl – who famously cultured notoriously fragile Hodgkin cell lines for the first time, opening up new worlds of research possibilities – seems to have exerted an almost gravitational force on the trajectory of Engert's career.

When Diehl moved from Hanover to the University of Cologne, to become director of the Department of Medicine and chairman of the German Hodgkin Study Group, Engert took up the offer to come with him – despite other offers to work in oncology, nephrology and immunology in Hanover. He worked with Diehl for two years, but when offered a six year contract, he again rebelled.

"I said I didn't want it – I want to go into research." That was when he spent two and a half years researching antibody-based immunotherapy for patients with malignant lymphoma under professor Philip Thorpe at the Imperial Cancer Research Fund in London: "It was a great time, to learn all the techniques and have time for science only." But then Thorpe went to Dallas. Engert didn't want to follow him to America but he did want to continue work on trialling the promising immunotoxin drugs he had helped develop in London. So in 1991 he decided to rejoin Diehl in

"It was a great time, to learn all the techniques and have time for science only"

Cologne, where as head of the laboratory of immunotherapy he could conduct phase I and II clinical trials on the new drugs – which ultimately proved disappointing.

Engert has remained there ever since, becoming deputy medical director in 1999, and taking over from Diehl as chairman of the GHSG in 2007. He fell in love with Cologne, he says. A sense of the city's scientific heritage hangs around the vast atrium of the University Hospital where he works, with photographs and memorials to the likes of medieval experimenter Albertus Magnus and heart radiography pioneer Friedrich Moritz.

As for the shadow of his predecessor, Engert has a pragmatic view – respectful, but clear that if things are to progress, past achievements have to be viewed as inadequate. There is little room for sentiment in medicine.

"I had had my own interest in immunotherapy for a long time and brought a lot of new treatment aspects into the group," he says. "I supported Volker and worked with him, and when he left the hospital and I took over, there were many things I maintained – but it was good for me to have more freedom to run things as I would have loved to before."

"Over these years the knowledge and experience of this group has broadened substantially," he says. "Volker's work allowed us to become one of the leading groups on this disease worldwide, and we really appreciate that. But things have evolved and adapted to modern aspects of treatment and how studies have to be done." The GHSG today recruits patients from more than 400 centres in five European countries.

The increasing influence of the group has led it into intense exchanges with other groups – debates about best treatment that Engert believes are extremely important for clinical progress, and which he admits to finding enjoyable. "It would be boring if everyone had the same opinion and there was no more development," he says.

One of the most important has been about what should be the standard chemotherapy regimen for advanced Hodgkin lymphoma. The debate, conducted over the past five years on the pages of the most high-powered professional journals, has seen the German group pitted against groups in America, the UK and Italy.

It started in 2004 when Engert and Diehl presented the findings of a major study which showed that the German group's BEACOPP regimen was 20% better at tumour control and 11% better for overall survival than current standard chemotherapy regimens revolving around ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). What is more, the benefits became clearer the longer patients were followed up.

But American study groups took issue: BEACOPP was too toxic for standard use, they

HODGKIN LYMPHOMA

Hodgkin lymphoma, also known as Hodgkin's disease, is a cancer found in the lymph nodes. Most commonly it starts in the lymph nodes of the neck. One in five lymphomas are Hodgkin.

Hodgkin lymphoma can affect people of any age, but it most frequently affects two groups: those aged 15–35, and those aged over 55.

It is characterised by the presence of Reed-Sternberg cells – B-lymphocytes that have become cancerous. Non-Hodgkin lymphomas do not have Reed-Sternberg cells.

The malignant cells are large – but they are widely scattered compared to other cancers. While in lung cancer or other lymphomas, pathology reveals a high density of malignant cells, Hodgkin cells are surrounded by benign 'bystander' cells. Research by Engert showed that if just the malignant cells are destroyed, the bystander cells disappear as well.

Until Volker Diehl first successfully cultured Reed-Sternberg cells in 1978, a significant barrier to researching the condition was the fragility of the malignant cells once removed from the body. Even today, when there have been over a quarter of a million attempts to culture Reed-Sternberg cells, there are only 14 cell lines in the world. Five of these were cultured by Diehl.

said. Engert acknowledges they had a point: it is more toxic than ABVD. But what these other international groups – the "anti-BEACOPP alliance" as Engert calls them – have failed to acknowledge, he claims, is that it is also much more effective.

Another study, published in the *New England Journal of Medicine* last July by Viviani and colleagues at the Istituto Nazionale Tumori in Milan, indicated that BEACOPP was 12% better at tumour control than AVBD. But, according to Engert, the article and accompanying editorial instead concentrated on the fact that overall survival with BEACOPP was no better than with the less toxic ABVD – "which is not surprising given the small number of patients in the study."

"They were basically saying this study showed that ABVD was as good as BEACOPP, which we think is unfair. We always said that BEACOPP is more toxic than ABVD. But we all have to stick to facts and not overshoot in our attempts to disprove one another."

The Istituto Nazionale Tumori meanwhile is emphatic that "we have not hidden or confused the message."

The debate is moving on again, with the German group providing evidence in a *Lancet* article this May that less toxic doses of BEACOPP are equally effective as larger doses. Engert is all too aware of the awkward balance between risk and benefit, acknowledging that sometimes a high risk is necessary whilst doing everything possible to minimise it.

What such debates reveal to Engert is the importance of following the patient's story for as long as possible after treatment, not jumping to conclusions after short-term studies. "The stories of terrible side-effects aren't over yet," he says. "Hodgkin's is a great teacher because you can follow patients carefully through to the end – the consequences of their treatment may not be visible for 20 or 30 years. We are certainly keen to get rid of chemotherapy and radiotherapy. However, this certainly cannot be done at the price of a very high relapse rate."

It is natural enough that patients, oncologists and indeed drug companies should want to concentrate on cure. But people who have been treated for Hodgkin's form the biggest cancer survivor group in Western countries, with 70–80,000 in Germany alone, so that researchers and

The Engert family circle

"We all have to stick to facts and not overshoot in our attempts to disprove one another"

"Pretty early on I realised that cancer patients give back a lot, they want to co-operate"

clinicians are able to look far beyond remission. Hodgkin's, says Engert, can serve as a 'model cancer', providing answers not just on side-effects, but also on how to support patients long-term through enduring problems such as infertility and fatigue.

This human element of the oncologist's role is important to Engert, who has always tried to balance laboratory work with clinical work. One of the reasons he went into oncology was that it seemed less mechanistic, more based on long-term relationships with people, than specialties such as cardiology. The relationship is not always a simple one, he acknowledges. Patients tend to focus solely on cure at the start of their journey, and oncologists have to be careful to counsel them about side-effects such as infertility, hair loss and fatigue that will become of major importance to them later. The complexity of some decision-making requires meaningful collaboration.

"Pretty early on I realised that cancer patients give back a lot," says Engert. "They realise they have to work with you, and want to co-operate. You see them develop in this respect, whereas in other areas such as cardiology, people are hardly off the intensive care unit after heart attack and they're off to work again, and there's no long-term working relationship with the doctor."

What about Engert's human side? Given the motivating role played by his father's experiences with cancer, how much does his own young family know about his work and what he is trying to do? Aged 53, married to an artist, he has four children aged between 10 and 17, and their photographs cover one wall of his office. He tries to devote as much time as possible to home life, but the demands of work and international conferences don't make this easy and sometimes he brings his children into work or takes them to conferences with him.

Sometimes he has his doubts about how much of his work his children really understand, but he does know that, among friends and family of the children's friends, there have been several with cancer who have asked Engert for advice. The children know about this and discuss it – there is no taboo around cancer. And Engert admits that he would be "honoured" if any of them decided to follow him into medicine. Perhaps that story too will come full circle.

If it does, the challenges his children face may be very different than Engert's. "I think this new drug, and others to come after it, will change treatment for Hodgkin's fundamentally," he says. Already well-tested in relapsed patients, brentuximab vedotin is now undergoing trials as a maintenance treatment, with the aim of reducing the number of relapses. Engert believes that in two years, therapy for relapsed patients will have changed substantially, and within a decade chemotherapy and radiotherapy will no longer be mainstays of treatment.

Does that mean everything is rosy? Not quite. For those who specialise in Hodgkin's, there is always the nagging worry about the unforeseen future – the worries about treatment side-effects that gave Volker Diehl sleepless nights. Engert too knows the risks that can come with new treatments. In 2006 he advised the biotech company Te Genero not to test its antibody TGN1412 on healthy volunteers – advice the company rejected. As a result, 10 volunteers in London suffered near-fatal side effects. "I told them it was nonsense to try this drug on healthy volunteers in this type of trial – you can't do this. But they did."

It all goes to show that there is no room for complacency in treatment development. "Drugs aren't like water," says Engert. "If we had a shiny new side-effect-free drug, and then a year after its introduction patients started dying from secondary cancer then, yes, I too would start having night sweats and nightmares."

For the moment, he is cautiously confident. But he knows only too well that the greatest arbiter of treatment success is time. ■

Testing the testers

MARC BEISHON

Treating the right patient with the right therapy at the right time depends on having the right picture of every patient's key biological markers. A number of initiatives are now springing up across Europe to ensure that the testers are indeed getting it right.

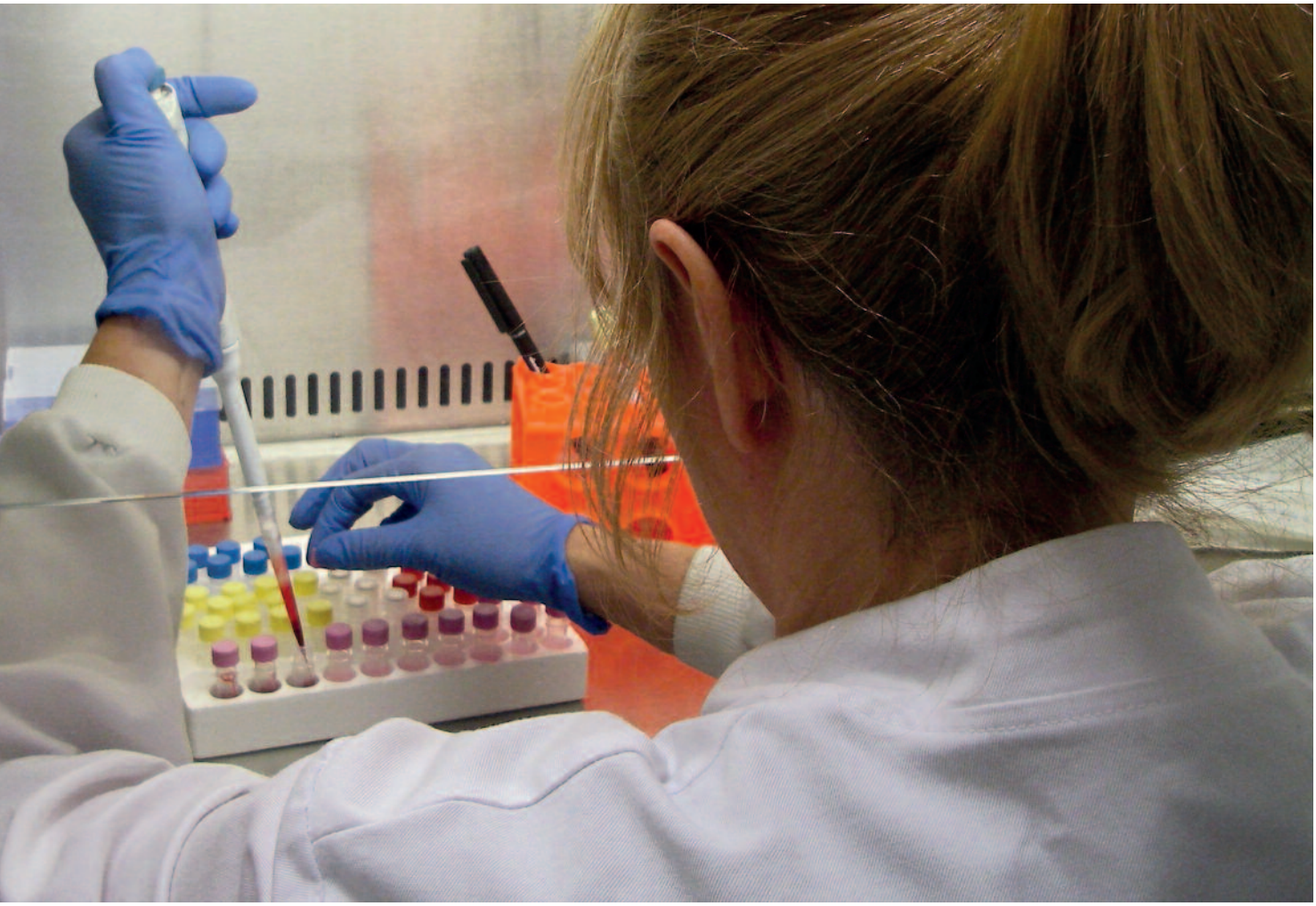
As the era of personalised medicine has developed, it has brought with it the need to conduct an increasing number of biological tests to determine the appropriate personalised therapy. Key examples are HER2 status for response to Herceptin (trastuzumab) and the KRAS mutation, which predicts for a poor response to EGFR inhibitors such as Erbitux (cetuximab).

Now the floodgates are opening, as increasingly sophisticated genetic testing of tumours is revealing a raft of gene mutations, dislocations and fusions that are the target of current or future drugs, notably in lung cancer, where in just a few years possible treatment options have changed dramatically. The sheer number of patients where molecular testing will be essential – such as the many with metastatic colon or lung cancer – is a big challenge now.

Cancer centres are pressing ahead with projects that carry out several assays on tumours to give more information to patients and their oncologists, and to identify people eligible to join clinical trials. At national level in countries such as France and the UK, cancer policy makers are rolling out and making preparations for the routine testing of a range of genetic mutations in the major cancers such as breast, colorectal and lung.

These projects highlight one of the big challenges with molecular biomarkers – ensuring that testing is carried out to a consistently high standard. As Cancer Research UK, which is organising the UK's Stratified Medicine Programme for a panel of genetic tests, comments about the earlier introduction of Herceptin, "Having to routinely, reliably and accurately test a breast tumour's HER2 levels, as part of 'business-as-usual', was uncharted territory for many pathologists."

Indeed, Giuseppe Viale, professor of pathology at the University of Milan, has written extensively about controversies in HER2 testing, and has noted that despite decades of experience with assays, and the availability of



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standardised reagents, kits and guidelines, "the accuracy and reproducibility of the test results are still a major concern worldwide". Results of several quality-control schemes for pathology laboratories have shown as many as 15–20% false-positives with immunohistochemistry testing, and there can also be a high error rate in another key testing method, fluorescence *in situ* hybridisation (FISH).

But it is also true that we still don't understand enough about the biology of breast cancer to be certain about how HER2 testing should best be carried out and interpreted. Tumours are not uniform in biology, and HER2 status may change over time. Uncertainty also remains about the right threshold values for predicting who could benefit from Herceptin. "Many oncologists seem to believe that pathologists are now infallible in assessing HER2 status of breast cancer," Viale notes, adding that it is frustrating that oncologists are pushing for more precise identification of targets for new agents in breast cancer while basic questions remain about HER2 testing (see Controversies in testing for HER2, ASCO 2011 Educational Book).

KRAS testing

The good news is that tests for other predictive molecular markers do not all suffer from the same complexity.

"Many oncologists seem to believe that pathologists are now infallible in assessing HER2 status"

"Our scheme has found a significant number of errors that could have had a big effect on therapy"

And although quality concerns are still very much to the fore, they have been tackled much more systematically in the case of KRAS, for example, as Han van Krieken, professor of pathology at the Radboud University Nijmegen Medical Centre, explains. "Indeed, HER2 testing is still far from optimal. One important reason lies in the biology. It is not completely known what factor is the most important for predicting trastuzumab response: the amount of protein or the regulation of the expression of the gene or the number of copies of the gene. The other important factor is that early on there was limited interest in the quality aspects. The situation with KRAS is very different: it is clear that activating mutations in the gene are the indicator and within two years of this discovery there was quality assurance."

KRAS mutations are important, because they occur in around 40% of patients with colorectal cancer, and they prevent EGFR inhibitors such as Erbitux and Vectibix (panitumumab) from working. As the large majority (almost 85%) of patients with colorectal cancer have tumours that overexpress EGFR, knowing who will and who will not benefit from an EGFR inhibitor is essential to avoid subjecting large numbers of patients to treatments that won't do them any good. Guidelines for using EGFR inhibitors therefore advise that testing for EGFR status alone is not enough; you also need to test for a variety of mutations in KRAS.

As van Krieken adds, not all of the 60% who do not have KRAS activating mutations will benefit, and there is not enough evidence yet to further separate out a target group from this majority. "But KRAS testing is common now – I don't think anyone is giving the anti-EGFR drugs in colorectal cancer without it." What has been critical, he says, is participation in quality assurance programmes at national and international levels, such as the European KRAS EQA (external quality assessment) scheme – a European programme he proposed with colleagues at the European Society of Pathology in 2008, and which is now in its fourth round.

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External quality assessment

Elisabeth Dequeker, the KRAS EQA scheme coordinator, who is based at the Biomedical Quality Assurance Research Unit in Leuven, Belgium, says the first step had been a pilot to establish regional laboratories that could prepare slides for the scheme – a quality control exercise in itself. These regional laboratories now send samples for which the KRAS mutation status is known, but not revealed, to laboratories participating in the scheme, to check they are getting accurate results. Between 2009 and 2011, 150 labs in Europe and in countries such as Indonesia and Israel reached a genotyping score of 90% or better in the scheme. "Some countries such as the UK and Germany also have their own national assessment schemes, but most smaller countries do not, and here in Belgium for several years now it is a requirement that all molecular oncology tests must be accredited. The best way of validating tests is with an EQA scheme," says Dequeker.

Given that there are several ways of testing for KRAS mutations, and also a choice of commercial kits and home-grown systems, the EQA scheme has not attempted to distinguish between approaches. "If you implement your methodology well and validate it according to standards your method will be stable," she says. "But molecular pathology is not easy and our scheme has found a significant number of errors that could have had a big effect on therapy."

Van Krieken reports that, from the first round of the KRAS EQA scheme, 85% of laboratories had a 100% score on the samples, but 15% still had a substantial number of mistakes. "One mistake is in selection of patient material – you need to have sufficient tumour in your samples, and you may need to enrich them by cutting out normal tissue. The other main problem was in interpretation of results – some labs were making mistakes even using commercial systems and were missing some of the mutations."

Some labs may have to pull out of molecular testing if they can't improve, says van Krieken, but the indications are that with the right quality and educational schemes in place there will be few that cannot make the grade. In 2009, the Italian Association of Medical Oncology and the Italian Society of Pathology and Cytopathology ran a KRAS quality scheme similar to the European one. It found that only two participating centres out of 59 failed a 100% pass rate, and those two also failed a retake, being unable to extract enough genomic DNA for the mutational analyses.

PREDICTIVE BIOMARKERS AND TARGETED THERAPIES

Biomarker	Cancer type	Drug	EMA approval
BCR-ABL translocation	Chronic myeloid or acute lymphoblastic leukaemia	Imatinib Dasatinib Nilotinib	2001 2006 2007
KIT and PDGFRA mutations	Gastrointestinal stromal tumours	Imatinib	2002
HER2 amplification	Breast cancer	Trastuzumab Lapatinib	2000 2008
HER2 amplification	Gastric cancer	Trastuzumab	2009
KRAS mutations	Colorectal cancer	Panitumumab Cetuximab	2007 2008
EGFR mutations	Non-small-cell lung cancer	Gefitinib Erlotinib	2009 2011
ALK translocation	Non-small-cell lung cancer	Crizotinib	Not yet approved*
BRAF V600 mutation	Melanoma	Vemurafenib	2012

*USA FDA approval obtained in 2011. Abbreviation: EMA, European Medicines Agency.
Source: F Nowak, J-C Soria and F Calvo (2012) *Nat Rev Clin Oncol* 9:479–486, reprinted with permission, © *Nature Reviews Clinical Oncology*

The Italian quality scheme sent samples with a particularly high (>70%) content of tumour cells, but the organisers said that the impressive results may also reflect the benefits of an ongoing networking programme (called KRAS aKtive).

Lung cancer mutations

The European Society of Pathology EQA scheme has this year been extended to non-small-cell lung cancer (NSCLC) in two phases, first just the ALK mutation, which has generated much interest in oncology, and then a second round covering ALK, KRAS and EGFR, says Dequeker. France, which has its own quality schemes, is collaborating with Leuven on validating EGFR and BRAF programmes – the latter, for advanced melanoma, is turning out to be quite a challenge.

"What we are finding is that each test has its own problems," says van Krieken. "For example, the quality of DNA in a skin cancer biopsy can be affected by melanin, and sensitivity issues are very important in lung cancer as samples can be small. Each test and tumour needs its own EQA programme – you cannot assume a lab doing well with KRAS in colon cancer will also do well with say BRAF for melanoma."

Rolf Stahel, professor of oncology at Zurich University Hospital, Switzerland, and a lung cancer specialist, comments that the diagnostic possibilities for NSCLC are becoming very complex, although so far only EGFR mutations are recommended for testing at

"You cannot assume a lab doing well with KRAS in colon cancer will also do well with BRAF for melanoma"

"And if we test for a huge string of mutations we may also get results we don't want to know"

the first-line stage by the ESMO consensus panel on NSCLC pathology and molecular testing, on which he serves. The targeted drugs on offer here are the EGFR blockers Iressa (gefitinib) and Tarceva (erlotinib), with others in the pipeline, and there is a sizeable population – 10–12% of those with NSCLC.

"Now ALK testing is also recommended, but in second-line treatment," says Stahel. "But here the testing is not easy as we don't have a final word yet on how best to test for it – will it be FISH, or immunohistochemistry and then FISH, or genetic sequencing. And it is in only about 5% of patients."

While ALK testing has now moved from the investigational stage into clinical practice, the key drug, Pfizer's Xalkori (crizotinib), was only recommended to receive conditional approval in Europe a few months ago, with the final decision still pending. Other mutations of interest, such as HER2, ROS1 and RET, are lower still in frequency, at 1–2%. This is now raising questions such as whether to prescreen with a cheap assay and then apply a more precise and expensive test on a subgroup. Stahel adds that testing is a "tremendously fluctuating field" as we move up the hierarchy from looking for single mutations, with traditional immunohistochemistry testing near the bottom, to more sophisticated tests such as FISH, to exome sequencing at the top – and indeed whole genome sequencing ultimately.

"And if we test for a huge string of mutations we may also get results we don't want to know," he says. "The pathologists here in Switzerland are gung ho about buying new sequencing machines – but how are we going to cope with the information in the clinic? How do we communicate results that are nothing to do with lung cancer?"

Stahel's own focus is very much on identifying the right clinical questions and ensuring high-quality testing. He leads the European Thoracic Oncology Platform (ETOP), which in its Lungscape project is analysing a large cohort of NSCLC tumours for a panel of molecular characteristics such as ALK, and which is playing a part in the European EQA scheme, among other activities. (For more on this, see Lungscape: a living lung laboratory, on p 44.)

A regional network

One potential way forward with lung cancer is outlined by Thomas Zander, a lung oncologist at Cologne University Hospital in Germany, who attracted attention at this year's ASCO with an abstract that described a regional screening network that has been set up for molecular testing of lung cancer patients at community hospitals in the Cologne-Bonn area. "The primary aim is to provide both well-established markers such as EGFR and ALK and also new diagnostics to community hospitals, so each lung cancer patient has the opportunity to know everything that is meaningful about their tumour," says Zander. He calls the process 'spreading' – running assays on a panel of mutations, so that patients have opportunities to participate in trials and to obtain new drugs before approval.

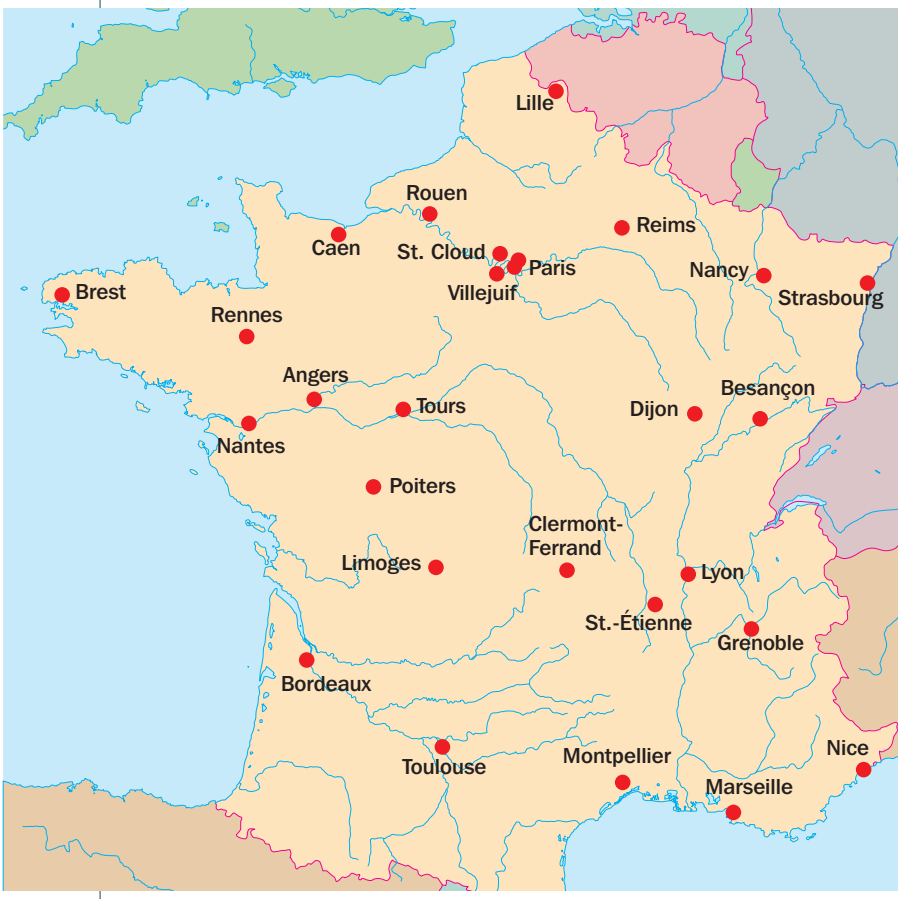
"Take ALK – it is not yet in routine clinical testing or treatment with crizotinib, but there is a consensus that if you test and find it you should treat. In Germany, although you have to ask specifically for reimbursement, we have not had a problem in a single case, which is a good indication that the health community agrees it should be done. What we can do then is make drugs such as crizotinib available a year or so before approval."

Crizotinib is being offered to patients via their primary oncologist, along with EGFR inhibitors, in Zander's area. Other mutations being tested in Cologne include BRAF, KRAS, PIK3CA and ERBB2, with 1750 samples being tested so far, estimated at 60–70% of NSCLC cases in the region. Obtaining the right quality of material for lung cancer diagnostics is much more of problem than with colon cancer, he says, given the difficulty of gaining enough tumour cells from a lung biopsy.

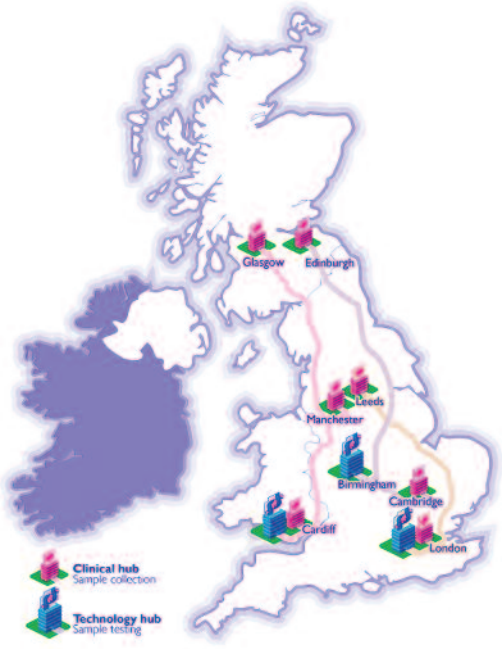
Zander adds that the lung cancer testing represents a step-change in the number of assays being performed, using the array of technologies currently available. "We started with four or five assays, and we are already up to 14, and in a few years it could be 40," he says. What is needed are technologies that 'multiplex' – measure simultaneously – the various mutations, and which home in only on those that are allowed to be searched for.

Zander agrees this is a challenge. "That's the great problem with new gene sequencing technologies – soon it will be cheaper just to sequence every-

NATIONAL TESTING PROGRAMMES



The French molecular profiling programme carried out 55,000 tests across 28 regional centres in 2011. The UK system is seeking to enrol 9000 patients with cancers that are treatable with targeted therapies, in the first stage of its Stratified Medicine Programme, as a pilot for introducing molecular profiling throughout the National Health Service



MAP OF UK: CANCER RESEARCH UK

thing, but for legal reasons we are not allowed to analyse anything else without asking the patient." So far, assays at Cologne do focus only on key lung mutations, he says, while data handling has not been an issue.

Cost is a major issue of course – outside of approved EGFR drugs there is no reimbursement for the often expensive diagnostics being done in Cologne, and Zander is reliant on grants.

National testing schemes

Meanwhile national schemes where centralisation is the theme are underway. Spain has taken early steps with demonstrating how national EGFR screening can work, as described in a much-cited paper from 2009 by Rafael Rosell and colleagues at the Spanish Lung Cancer Group (see Screening for epidermal growth factor receptor mutations in lung cancer; *NEJM* 361:958–967).

France probably has the most advanced national molecular profiling programme in Europe. Running for four years now, the French National Cancer Institute (INCa) and the Ministry of Health have set up a national network of 28 regional molecular genetics centres that carry out not just predictive tests such as for HER2, EGFR and KRAS status, and mutations

"Obtaining the right quality of material for diagnostics is much more of problem with lung than with colon cancer"

"The key aim is to show how quality-assured molecular testing can be done, linked to bioinformatics, at a low cost"

in leukaemia and GIST that predict for response to Glivec (imatinib), but also diagnostics for factors such as chromosomal abnormalities in sarcomas and lymphomas, and prognostic tests to guide treatment in tumours such as neuroblastoma.

An idea of the scale is given in a paper by Frédérique Nowak and colleagues: in 2012, an estimated 40,500 patients will be diagnosed with colorectal cancer, of whom 17,500 will need to be tested for KRAS mutation status, which will be provided free of charge to patients and hospitals, with compensation to local pathologists who have to ship the tumour blocks to the regional centres. In 2011, more than 55,000 predictive tests were carried out in total, mainly in leukaemia, breast, colorectal and lung cancers.

The centres are also preparing the ground for the fast introduction of new agents, as Zander's project is doing for lung cancer. A new-therapy programme is targeting biomarkers that are already in use in clinical trials. It was launched first for melanoma, lung and colorectal cancers – lung samples, for example, are being screened not just for EGFR but also for BRAF, KRAS, P13KCA, ALK and HER2, while an INCa-funded lung cancer database aims to make the most of linking molecular results with clinical and follow-up data.

Nowak and colleagues note too that "molecular tests performed on solid tumours are plagued by various sample-related and methodological problems" and that testing labs face a "permanent evolution of their daily practice", which is challenging for those that are not research institutions. This is blurring the distinction between service provision and translational development, and needs the joint input of pathologists, molecular biologists and clinicians (for more on this see Tumour molecular profiling for deciding therapy – the French initiative, *Nature Rev Clin Oncol* 2012, 9:470–486).

The UK also has an ambitious project in the Stratified Medicine Programme, headed by James Peach at the major charity, Cancer Research UK, with industry support. Many thousands of solid tumour tests are already being carried out in UK clinics, in particular EGFR and KRAS, but Peach says the project will show how they can be done collectively, mixing "say KRAS for colorectal cancer with BRAF and other markers to give a care choice to clinicians or accrual to a clinical study for researchers. We want to prove that standard tests such as KRAS can be linked to others in a single panel test," he says.

In the first phase of the programme, surplus material is being taken at hospitals with consent from about 9000 people with breast, colorectal, lung, prostate, ovary or melanoma tumours, which will be tested for about 20 mutations at three laboratories (over 2600 patients had enrolled in the programme by June 2012). The data will also be entered into a registry database alongside clinical outcomes. The key aim is to demonstrate to the UK's NHS how quality-assured molecular testing can be done, with associated bioinformatics systems, at a low cost – the sum of £300 (€380) or less is mentioned for delivering a result that could have several markers.

Again, cost in the UK, as in other health services, is a sensitive issue – industry has stepped in to fund testing in the NHS and in other countries to support oncologists who were finding it hard to organise tests even for approved drugs. Merck Serono, for example, has been paying for KRAS tests to pave the way for Erbitux, while AstraZeneca initially funded EGFR tests for Iressa in the UK.

Peach says the UK is going through a similar learning curve to other countries in testing for mutations such as KRAS, and quality assessment schemes are currently underway from the UK National External Quality Assessment Service (NEQAS). A BRAF pilot for melanoma has also started. Networking with other countries, such as France, will be important, and also with industry.

While oncologists and pathologists try to digest this already challenging agenda, the information about cancer mutations just keeps on coming. In July this year, researchers at the Cancer Genome Atlas in the US published in *Nature* a 'comprehensive molecular characterisation of colorectal cancer', finding no fewer than 24 significant mutated genes. And in September, the Cancer Genome Atlas also found that half of squamous cell lung cancers, for which there are no current targeted therapies, have mutations that may be susceptible to current or new drugs – some of these no doubt will soon be added to Europe's expanding molecular testing programmes. ■

Late diagnosis

Why does it happen? How can we do better?

Patients whose cancers are diagnosed late are more likely to require treatments that are more debilitating, more expensive, and yet less likely to result in a cure. With experts in countries such as Denmark and the UK now identifying earlier diagnosis as key to improving their cancer outcomes – with the potential to prevent an estimated 5000–10,000 deaths a year in the UK – the spotlight is falling on general practitioners, and their capacity to accurately spot suspicious symptoms and fast-track patients for further investigations or specialist consultations. International studies have identified the most common themes associated with delayed referral across cancer sites as "misdiagnosis, occurring either through treating patients symptomatically or by relating symptoms to a health problem other than cancer… and a failure to fully or adequately examine patients, use of inappropriate or inadequate tests, and receiving or failing to follow up inconclusive negative or false-negative test results" (*Br J Cancer,* 101:S92–S101). But GPs see several hundred patients with potential cancer symptoms every year, of whom only a handful will turn out to have the disease. They often face pressure not to overload specialists and diagnostic services unless there is a very strong basis for suspicion. Is it fair to lay the blame for late diagnosis on GPs? *Cancer World's* Anna Wagstaff asked two experts – a general practitioner and a specialist in gastrointestinal cancer – to discuss the issue.

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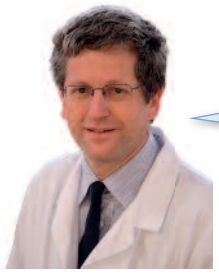
Further complicating this picture is that many of the patients who seek help most often from their GP are unjustifiably anxious about having a serious disease, and may want to have tests done when there is no good reason. This anxiety can seriously affect their wellbeing, and their fears are often heightened rather than allayed by being tested. But of course these patients may suffer from cancer just like anybody else. So GPs as well as the health care systems are faced with real dilemmas here.



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I agree that symptoms in cancer sometimes appear late and are often atypical, which is why they are recognised by the patient or the physician late. And when GPs are presented, for example, with functional abdominal symptoms – vague abdominal pain, a little anorexia, some dyspepsia – it can be difficult for them to filter those that might be related to a cancer from those that are not. However, sometimes there is a problem with inadequate examination. For instance, in the case of colon cancer, a patient may report rectal bleeding; the doctor sees the patient has haemorrhoids and concludes, "OK, it is probably linked to the haemorrhoids and it would not be appropriate to examine the colon." So they decide not to test. Or when tests are done, they don't always use the most appropriate ones. For instance, in patients with dyspepsia and a little bit of weight loss, they may do an ultrasound of the pancreas; they find nothing, and they say the pancreas looks good. But ultrasound does not have perfect sensitivity – a CT scan is better in this situation. With some tests and examinations, physicians sometimes do two or even three screening examinations where nothing is shown, because of the lack of sensitivity.

So the problems are not doing the appropriate test, not going far enough with some patients, and in other patients doing a first test with a lower sensitivity and then taking the decision – OK let's wait a couple of months, and if it deteriorates we will go further.

It's true that there can be psychological downsides to testing. But not being tested when you have symptoms can cause greater anxiety. And failing to rule out cancer as a possible cause of symptoms could have greater consequences than creating anxiety. You have to weigh the risks against the benefits.

GPs can of course make mistakes like the one you mention and fail to investigate further the cause of blood in the faeces because they assume it must be explained by the presence of haemorrhoids. But it may also be that the patient is reluctant to be tested.

I would have to recommend a colonoscopy, which for the patient involves a day of liquid food and laxatives to empty the colon, and then being investigated quite far up through the rectum. It is not always easy to get patients to accept this unless they really feel there is a serious risk.

With patients whose intestines usually function like clockwork, it can be obvious when something is wrong. But a lot of people have benign colon symptoms most of their life, which fluctuate up and down, and that can hide more serious changes. You have to look for things like weight loss, or maybe new forms of dyspepsia that the patient didn't have before. Sometimes watchful waiting is the only thing you can do if a patient is not willing to go further and your suspicion is quite weak. You can take a blood test to check haemoglobin levels and then ask them to monitor their weight and their symptoms and come back for further testing.

The lack of specific symptoms can also be a problem when it comes to referring patients for CT scans of the pancreas. Pancreatic cancer can be difficult to spot because there are so few specific alarm symptoms unless the patient looks jaundiced. There may be unspecific pain in the upper abdomen, which could be due to many reasons, some of them quite common. In Denmark, GPs cannot refer patients directly for a CT scan. We can refer them using a new fast-track cancer diagnosis scheme, but you would need a strong enough suspicion to use that option.

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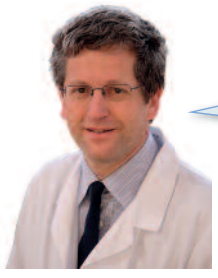

Access to CT scanning will depend on the resources and system in each country. It's true that in some countries access can be difficult, but in other countries CT scans are overused. In Belgium it is not difficult to get patients referred for a CT scan, but there is still a judgement problem – people can make the call too late. It is essential to correctly evaluate the severity of the symptoms.

Regarding patients' reluctance to undergo a colonoscopy, there is a great problem with the public perception of this examination. There is no alternative and it needs to be demystified so that people are less resistant.

Doctors need to take time to explain what is involved and that the patient has a lot more to gain than they have to lose. The most difficult part is the preparation, and doctors need to explain carefully how this should be done, because the colonoscopy itself will be much more difficult if the colon has not been adequately cleared. If it is well done the patient experience is not too bad. Information and communication are key, as well as good quality control.

I agree that good information and communication are essential, and you need to take time to build up a good picture of the symptoms and risk factors. This in itself can be a problem, particularly in countries like the UK where GPs are meant to spend no more than 10 minutes with each patient. It also takes time to talk to patients about why you think they may need further tests. When we first started referring patients to the fast-track cancer diagnosis, it took a while to get used to those conversations – at first it seemed a little harsh. Before, you would only raise the possibility of cancer with patients where there were stronger reasons for suspicion. Now we have to say, "We have this suspicion, which is not very serious, but we want to make sure, so I will send you now." You need to adapt your communication, so you don't scare people, but help them understand that it is a fast way to most probably find out that there is nothing wrong. If it is a cancer, it will be found earlier. It is also important to make sure that, after they have been through the fast cancer track, whatever the outcome is, they either call or come back for an evaluation or chat.

IT systems may also have a role to play in reducing late diagnosis. There may be a combination of diagnosis coding, data capture and aids to diagnosis that in the quite near future may help GPs. In Finland they are working on a decision-making software that could help GPs be more systematic in reaching a diagnosis. While you are in consultation with a patient you can enter the symptoms on your computer and will get suggestions about possible diagnoses and other questions or investigations you can do. So, for instance, if you have unspecific pain in the upper part of the abdomen, you could be prompted to think: pancreatic cancer. IT systems can also make it easier to refer patients for diagnostic tests. Linked data systems can provide information about the local options for referrals, they can enable you to make the referral electronically, and the use of standardised criteria can ensure that only people who need referral will get it.

GPs have a crucial role in diagnosing cancers early. If GPs feel they don't have enough time, they need to raise this within their health system and get changes. I understand it is very difficult for them. Specialists have very in-depth knowledge, but about many fewer things. GPs, in contrast, have to know about a wide range of things – not only all the different cancers, but everything else like diabetes and heart disease. Good interaction between specialists and GPs may help – I spoke to 200 GPs recently on the issue of familial risk, screening and other topics at an evening meeting and they clearly welcomed the chance to learn more.

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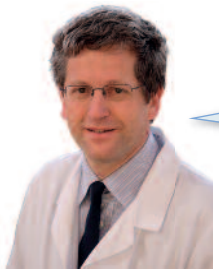

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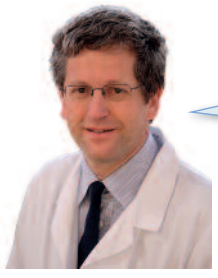

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The origin of a special success

CLIVE COOKSON

Cancer genetics is intriguing, exciting and offers hope for real progress in treatment, but try telling that to non-scientists. Clive Cookson, science editor at the *Financial Times*, did just that. His article, explaining the evolutionary process that drives cancer, won him a Best Cancer Reporter Award.

Cancer scientists have a new patron saint: Charles Darwin. Research is showing that the only way to cure cancer in its many forms will be to understand the Darwinian evolution that drives the disease within each patient, as natural selection works on genetic mutations within tumour cells.

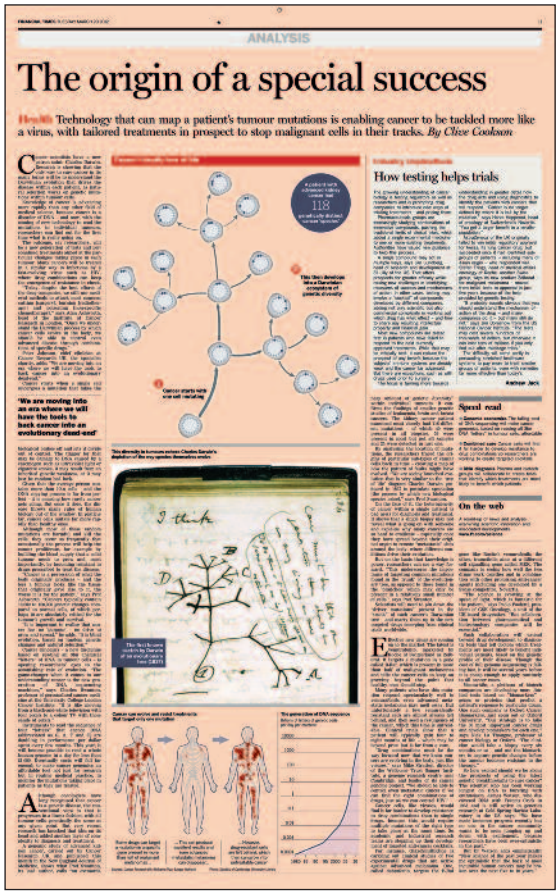
Knowledge of cancer is advancing more rapidly than any other field of medical science, because cancer is a disorder of DNA – and now, with the coming of new technology to read the mutations in individual tumours, researchers can find out for the first time what is really going on.

The outcome, say researchers, will be a new generation of tests and personalised treatments aimed at the particular changes taking place in each tumour. Many cancers will be treated in a similar way to infections by a fast-evolving virus such as HIV, where drug combinations can keep the emergence of resistance in check.

"Today, despite the best efforts of the drug companies, we still use medieval methods to attack most cancers: cutting [surgery], burning [radiotherapy] and poisoning [non-specific chemotherapy]," says Alan Ashworth, head of the Institute of Cancer Research in London. "Once we understand the Darwinian process by which cancer cells evolve in the body, we should be able to control even advanced disease through combinations of specific drugs."

Peter Johnson, chief clinician at Cancer Research UK, the specialist charity, adds: "We are moving into an era where we will have the tools to back cancer into an evolutionary dead-end."

Cancer starts when a single cell undergoes a mutation that takes the biological brakes off and lets it divide out of control. The trigger for that may be damage to DNA caused by a carcinogen such as ultraviolet light or cigarette smoke, it may result from an inherited genetic weakness, or it



ANALYSIS

The origin of a special success

Health Technology that can map a patient's tumour mutations is enabling cancer to be tackled more like a virus, with tailored treatments in prospect to stop malignant cells in their tracks. *By Clive Cookson*

How testing helps trials

Spool read

On the web

'We are moving into an era where we will have the tools to back cancer into an evolutionary dead-end'

FT

FINANCIAL TIMES

Clear, accurate and stimulating stories like this one help sustain the public's trust and belief in scientific and medical research

may just be random bad luck.

Given that the average person contains more than 10 trillion cells – and the DNA copying process is far from perfect – it is amazing how rarely cancer gets going. But once it does, the disease throws many rules of human biology out of the window. In particular, cancer cells mutate far more rapidly than healthy ones.

Although most of these random mutations are harmful and kill the cells, they occur so frequently that occasionally the process will help the cancer proliferate, for example by building the blood supply that a solid tumour needs to grow and, most importantly, by becoming resistant to drugs prescribed to treat the disease.

"Cancer is a perversion of what the body originally produces – and the less a tumour looks like the tissue that originally gave rise to it, the worse it is for the patient," says Prof Ashworth. "Cancers typically contain 10,000 to 100,000 genetic changes compared to normal cells, of which perhaps 10 are absolutely critical for the tumour's growth and survival.

"It is important to realise that cancer has no 'purpose' – no drive to grow and spread," he adds. "It is blind evolution, based on random genetic changes and natural selection."

Cancer genomics – a new discipline based on reading all 3 billion chemical 'letters' of DNA in tumour cells – is opening researchers' eyes to the astonishing rate of evolution. "The game-changer when it comes to our understanding cancer is the new generation of DNA sequencing machines," says Charles Swanton, professor of personalised cancer medicine at the University College London Cancer Institute. "It is like moving from a black-and-white television with four pixels to a colour TV with thousands of pixels." Instruments to read the sequence of four 'letters' that encode DNA (abbreviated as G, A, T and C) are doubling in performance per dollar spent every few months. This year, it will become possible to read a whole human genome in a day for less than $1,000. Eventually costs will fall far enough to make cancer genomics an affordable tool not just for research but in routine medical practice, to monitor the mutations taking place in patients as they are treated.

Although oncologists have long recognised that cancer is a genetic disease, the conventional view is that it progresses in a linear fashion, with all tumour cells genetically the same at any given point. But very recent research has knocked that idea on its head and added another layer of complexity to diagnosis and treatment.

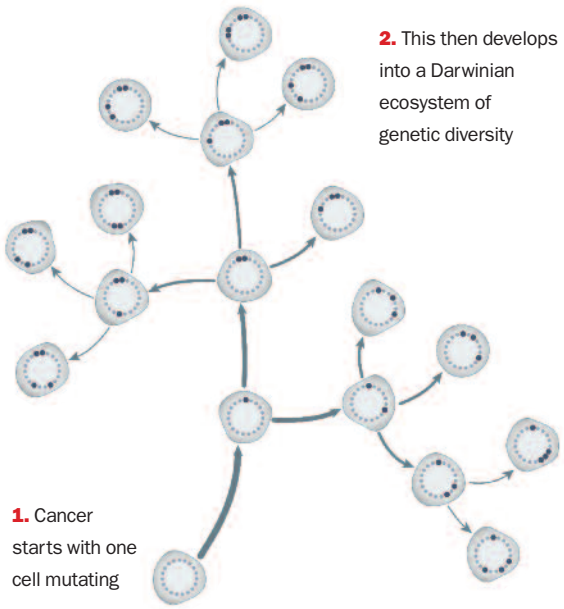
A genomic study of advanced kidney cancer, carried out by Cancer Research UK and published this month [March 2012] in the *New England Journal of*

"We are moving into an era where we will have the tools to back cancer into an evolutionary dead-end"

"We are seeing branched evolution very similar to the 'tree of life' diagram Charles Darwin produced in 1837"

CANCER'S DEADLY TREE OF LIFE

A patient with advanced kidney cancer had 118 genetically distinct cancer 'species'. This diversity in tumours echoes Charles Darwin's depiction of the way species themselves evolve.



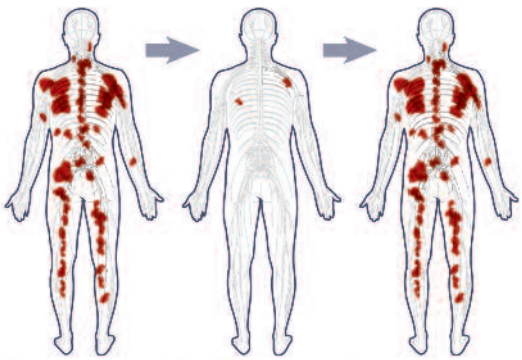
1. Cancer starts with one cell mutating

2. This then develops into a Darwinian ecosystem of genetic diversity

Medicine, shows what Prof Swanton, its lead author, calls "an extraordinary amount of genetic diversity" within individual tumours. It confirms the findings of smaller genetic studies of leukaemia, brain and breast cancers. The kidney cancer patient examined most closely had 118 different mutations – of which 40 were present in all biopsies, 53 were present in most but not all samples and 25 were detected in just one. By analysing the location of mutations, the researchers traced the origins of particular sub-types of cancer cells back in time – creating a map of how the pattern of faults might have evolved. "We are seeing branched evolution that is very similar to the 'tree of life' diagram Charles Darwin produced in 1837 to postulate speciation [the process by which new biological

The first known sketch by Darwin of an evolutionary tree (1837)

Cancer can evolve and resist treatments that target only one mutation



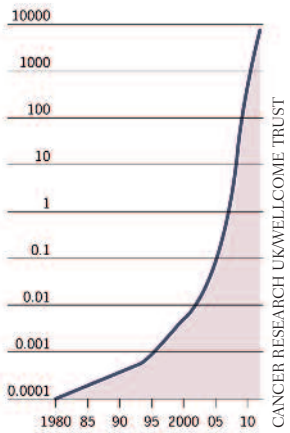
Some drugs can target a mutation in a specific gene present in more than half of malignant melanomas ...

... This can produce excellent results and even advanced metastatic melanoma can disappear...

... However, drug-resistant cells are left behind, which then can grow into untreatable cancer

The generation of DNA sequence

Billions of letters of genetic code per day per machine



CANCER RESEARCH UK/WELLCOME TRUST

species arise],” says Prof Swanton.

On the face of it, the heterogeneity of cancer within a single patient is bad news for diagnosis and treatment. It shows that a single biopsy may not reveal what is going on with someone and explains why many cancers are so hard to eradicate especially once they have spread beyond their original organ to remote ‘metastatic’ sites around the body, where different conditions drive their evolution.

But on the basis that knowledge is power, researchers can see a way forward. “This underscores the importance of targeting common mutations found in the ‘trunk’ of the evolutionary tree, as opposed to those found in the ‘branches’ which may only be present in a relatively small number of cells,” says Prof Swanton.

Scientists will need to pin down the ‘driver mutations’ present in the ‘trunk’ of each cancer’s Darwinian tree – and marry them up to the new targeted drugs emerging from clinical trials worldwide. Effective new drugs are coming on to the market. The latest is vemurafenib, marketed by Roche of Switzerland as Zelboraf. It targets a mutation in a gene called B-Raf, which is present in more than half of malignant melanomas and tells the cancer cells to keep on growing beyond the point that healthy ones should stop.

Many patients who have this mutation respond spectacularly well to vemurafenib; even advanced metastatic melanoma may melt away. But unfortunately a few vemurafenib-resistant cells are almost always left behind, and they seed a resurgence of the cancer, which this time is untreatable. Clinical trials show that a patient will typically gain four to eight months of life – which may be beyond price but is far from a cure.

“Drug combinations must be the way forward now that we know cancers are evolving in the body, just like viruses,” says Mike Stratton, director of the Wellcome Trust Sanger Institute, a genome research centre near Cambridge, and leader of its cancer genome project. “We should be able to control even metastatic cancer if we can find the right combinations of drugs, just as we can control HIV.” Cancer cells, like viruses, would find it far harder to develop resistance to drug combinations than to single drugs, because this would require multiple mutations of the right type to take place at the same time. So academic and industrial research teams are stepping up their development of targeted anti-cancer cocktails.

For instance, GlaxoSmithKline is carrying out clinical studies of two experimental drugs that are active against advanced melanoma. One, called dabrafenib, targets the B-Raf gene like Roche’s vemurafenib; the other, trametinib, aims at a different cell signalling gene called MEK. The company is seeing how well the two drugs work together and in combination with other promising anti-cancer agents including one developed by a Swiss competitor, Novartis. “The science is evolving at the speed of light, which is fantastic for the patient,” says Paolo Paoletti, president of GSK Oncology, a unit of the UK-based drugmaker. “But collaboration between pharmaceutical and biotechnology companies will be essential.” Such collaboration will extend beyond drug development to diagnostic tests that tell doctors which treatments are most likely to benefit individual patients, based on the genetic profile of their disease. Though the cost of full genome sequencing is falling fast, it will be several years before it is cheap enough to apply routinely to all cancer cases.

Meanwhile, a plethora of biotech companies are developing more limited tests based on ‘biomarkers’ – genes or proteins that predict a patient’s response to particular drugs. One such company is Oxford Cancer Biomarkers, just spun out of Oxford University. “Our strategy is to take the 30 most important cancer drugs and develop biomarkers for each one,” says Nick La Thangue, professor of cancer biology at Oxford. “The clinician would take a biopsy every six months or so – and use the biomarkers to capture genetic changes before the tumour becomes resistant to the therapy.”

So how excited should we be about the prospects of using the latest genetic breakthroughs to cure cancer? The scientist who has been working longest on DNA is bursting with enthusiasm. James Watson, who discovered DNA with Francis Crick in 1953 and is still active in genetics research at Cold Spring Harbor Laboratory in the US, says: “We have made immense progress recently but no one in the cancer community wants to be seen jumping up and down with excitement, because researchers have been over-optimistic in the past.”

But Dr Watson adds emphatically: “New science of the past year makes me optimistic that the back of most incurable human cancers may be broken over the next five to 10 years.” ■

This article was first published in the *Financial Times* on 20 March 2012, and is reprinted here with permission. © Clive Cookson

“The science is evolving at the speed of light, which is fantastic for the patient”

OECI accreditation: is yours a top-class cancer centre?

Whether you work at a cancer unit, a cancer centre or a comprehensive cancer centre, applying for OECI accreditation is a good way to find out how your institute compares with the best, and get advice on how to address any shortcomings.

The fragmentation of academic research is a major organisational problem in Europe. There is also a clear need to improve translational research and to overcome differences experienced by patients across Europe in access to diagnostics and treatment, which feed into disparities in therapeutic outcomes.

To address these issues, the Organisation of European Cancer Institutes (OECI) – a body dedicated to improving research collaboration among Europe's cancer centres – identified the need to develop a system for monitoring the research and care offered to patients, and also to find ways to harmonise patient care and share the knowledge that we are developing to improve the standard of care. To this end, the OECI developed a tool for assessing and benchmarking the care and research being carried out in cancer centres.

The challenge for cancer centres is to meet all the requirements of the

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*. In this issue, Mahasti Saghatchian, of the Institut Gustave Roussy, in Villejuif, France, reviews the OECI programme for accrediting cancer centres, which she helped develop and now chairs. Gordon McVie, from the European Institute of Oncology in Milan, Italy, poses questions arising during the live presentation. It is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, is available at www.e-eso.net

different stakeholders (see figure). The key stakeholder is the patient, and a central aim for any cancer centre is to provide patients with the best care. The challenge for the OECI was, first and foremost, to develop a tool that would allow a cancer centre to ensure it was achieving this aim. Cancer centres are also answerable to health authorities, and we wanted to develop a tool that would help centres to collect an evidence base to prove they are providing good-quality care.

We also wanted the tool to help build the trust of cancer professionals and other organisations in the care and research being performed by cancer centres. Building the evidence base on the performance of each cancer centre could strengthen this trust. Finally, funders, including industry and the health authorities, want data on activity, outcomes and production in terms of activity. We wanted our accreditation system to be able to help cancer centres provide this.

A supportive approach

Most quality assessment programmes are regulatory measures imposed by an external authority, and are usually compulsory. We developed the OECI quality assessment programme as a supportive measure for cancer centres, and it is voluntary. It has been designed and developed internally by people from cancer centres. Peer review is performed by people from cancer centres and visits are chaired by the director of another cancer centre. The standards that we have set have been developed and are revised every four years by people from the centres.

Gordon McVie [GM]: *You work at the Gustave Roussy, one of the most prestigious cancer centres in Europe. Why does your centre want to get OECI accredition?*

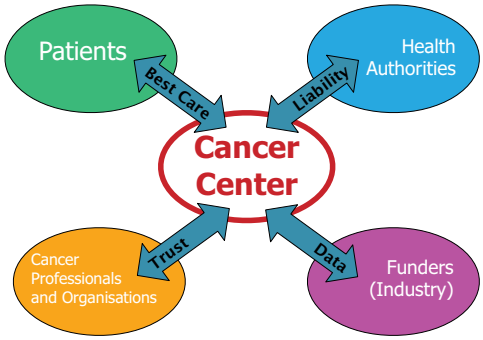
Mahasti Saghatchian [MS]: *We like to think we are one of the best, but when we entered the programme we still felt anxious about people visiting us. We prepared for the accreditation and visit very seriously and found it a very rewarding experience. Having a group of auditors visit us and assess what we do from an external point of view was reassuring. It is not enough to claim that you are a comprehensive cancer centre, you need to prove it to your peers and collect the necessary evidence.*

Gordon McVie [GM]: *It's a little bit like submitting research to a journal. As an author you think your research paper is great, but we need other people to look independently and assess its value.*

MS: *Different countries have different assessment and accreditation systems in place. In France we have mandatory accreditation for hospitals in general, but not specifically for cancer centres. Here at the Institut Gustave Roussy, we are going to be the only cancer centre accredited by the OECI.*

GM: *The process is similar to that which the US cancer centres have gone through, and provides a great deal of credibility.*

THE CANCER CENTRE CHALLENGE



Cancer centres have to satisfy the requirements of many stakeholders, primary among them being patients

Trust us: we're accredited. Wim van Harten, director of the NKI cancer centre in Amsterdam, shows his OECI certificate, flanked by former OECI president Marco Pierotti (left) and Mahasti Saghatchian, chair of the OECI Accreditation and Designation committee (right)

The OECI tools

The main tools that the OECI has developed are the accreditation and designation programme and the EurocanPlatform Network of excellence, both of which are supported by the European Commission and focus more on centres dedicated to translational research.

In the accreditation and designation programme, we have developed a tool similar to other accreditation programmes in its design, with a set of quantitative and qualitative standards integrated in a database, a report and a peer review system. The programme operates at three levels: the comprehensive cancer centre, the cancer centre, and the cancer unit. A pilot among OECI centres showed these are the three most frequent types of centres. We developed specific criteria for each of these. The programme includes standards and a database with a set of qualitative and quantitative data. We write a report and an improvement plan for each centre, which are reviewed by the accreditation board and then discussed with the centre.

OECI ACCREDITATION AND DESIGNATION 2012

- ✔ **Board - Management Unit - Accreditation Committee**
- ✔ **Qualitative and quantitative questionnaires - Designation criteria**
- ✔ **Electronic platform (e-tool) and website - Newsletter**
- ✔ **OECI Auditors**
- ✔ **For each cancer centre in the programme**
  1. Quantitative and qualitative data
  2. Report
  3. Improvement plan

Developing the programme

The accreditation programme has been running now for 10 years. The idea was first discussed in 2002. Then in 2005 the project was launched as an accreditation programme setting standards for cancer centres. Subsequently we realised that this was not sufficient and we would need different assessments for different types of centres, differentiating between larger or smaller centres for care or research and comprehensive cancer centres. We then developed the criteria that allowed us to have a designation system for the cancer centres, and launched the merged accreditation and designation programme in 2008.

We are at the end of the first version of the accreditation and designation programme and will be launching the second version of the programme in 2013. The standards are currently being revised and we are reviewing the quantitative data that we ask centres to provide. We are also working on a specific programme for prostate cancer centres in collaboration with the European School of Oncology, which has developed guidelines for prostate units. The OECI is now turning these guidelines into an accreditation system for prostate cancer units.

The OECI accreditation and designation programme is run by a board of people from cancer centres and has a management unit of people paid by the OECI to coordinate and run the programme (see figure above). There is also an accreditation committee, with 10 people from various cancer centres, which is chaired by Chris Harrison from the Christie Cancer Centre in Manchester, UK. This committee reviews all the reports provided by the auditors and makes recommendations to the board.

The programme uses a set of quantitative and qualitative questionnaires, which are currently being revised. These are integrated into an electronic tool available with a username and password and there is also a manual in paper format. When a centre participates in the programme, all answers to the questionnaires are entered into the database. A group of auditors, all from OECI cancer centres, carry out peer review visits.

Participating centres

Centres from all over Europe are taking part in the OECI programme. The first centres to enter the programme were in Portugal. Their health ministry asked all cancer centres to participate in an international accreditation programme and, after discussing whether to follow the US or European accreditation programmes, three centres opted for the OECI programme. Comprehensive cancer centres, smaller cancer units and university centres have all taken part in the OECI programme, and experience has shown it is applicable in all of these types of centres.

Of note, the Italian Ministry of Health has decided to fund all comprehensive cancer centres in Italy to go through the OECI accreditation programme. The nine Italian centres will go through the programme over two years. We think this is a good example of a country deciding to go for a European accreditation programme, and Italy is pioneering this.

GM: *How are different types of cancer centres defined? I know about comprehensive cancer centres because I am based at one in Milan. The European Institute of Oncology has a hospital and a large laboratory and patients are seen by*

multidisciplinary teams, so we are a comprehensive cancer centre. The Christie cancer centre, in Manchester, and the NKI-AVL, in Amsterdam, have similar facilities. Is the IPO [Instituto Portugués de Oncologia] in Lisbon a comprehensive cancer centre or a cancer centre?

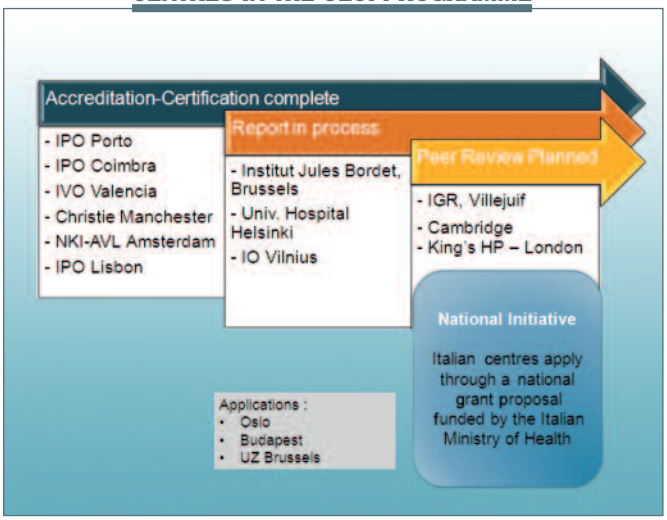
MS: *It is a cancer centre, but not a comprehensive centre, because it does not have enough research activities.*

GM: *Then what is a cancer unit? Have you looked at the cancer unit at the University Hospital of Helsinki?*

MS: *None of the centres currently in the programme is a cancer unit. We are currently in a one-year pending period for Helsinki. They applied as a comprehensive cancer centre, but it appears that they are a cancer department in a large hospital. Although they have a large amount of research and their research is of high quality, we considered that their research and care was not sufficiently integrated, and that their management and strategy in oncology were not clearly separated from the rest of the work of the university hospital. We considered that Helsinki could not be designated as a comprehensive cancer centre because they did not have the organisation, strategy or logistics of a comprehensive cancer centre. We offered them a one-year pending period to reorganise and develop the processes needed to achieve these.*

GM: *This strikes me as a very important example of the last part of the whole accreditation programme – the improvement plan. Cancer centres really appreciate that these accreditation visits are not just about checking that everything is OK or being critical, but are about saying, 'This is how you are now, what are you going to do to make things even better?'*

CENTRES IN THE OECI PROGRAMME



Focus of the programme

The accreditation programme focuses on what is critical to cancer care. This includes:

- planning and organisation of integrated care
- multidisciplinary teams and care
- integration and translation of clinical and basic research into care
- education for professionals
- the experience and involvement of patients
- monitoring and organisation of quality improvement.

The accreditation process

Application and designation screening

When a centre applies to the programme, the first step is to define whether you are applying as a cancer unit, a centre or a comprehensive cancer centre. Comprehensive centres have to provide data related to research, while cancer units and centres do not. Differences are otherwise based on volume of infrastructure, budget and activities. All centres then complete a self-evaluation period providing the required information, and the OECI makes a 'go or no-go' decision, advising the board on whether a centre is ready for peer review based on the information provided. This process avoids organising a peer review in a centre that is not ready.

Explanatory visit

An explanatory visit takes place immediately after the application and ensures that everyone in the centre is aware of the process, what will happen, and the information required. The OECI helps centres develop an action plan. We have found that centres have to dedicate one full-time person for a six-month period to collect the required documents and data.

Self-assessment period

In the self-assessment period, centres are required to collect documents, annual reports and data on quality, education, comprehensiveness and patients. It usually takes at least six months. We have found that gathering data on research activities is particularly difficult.

Electronic self-assessment tool

The e-tool includes a quantitative and the qualitative questionnaire. Qualitative questions are scored to assess the centre's degree of compliance to the standards, which are as detailed as possible in each question. Centres are asked to send reports or documents to support their answers. These can be uploaded onto the system. The tool automatically shows the centres any criteria where they are not fully compliant with the required standards, and helps to build improvement plans. Quantitative questions ask for numbers relating to infrastructure, resources etc. Once all the figures have been

submitted, the auditors review all the data, and then prepare for their visit.

Peer review visit

Trained auditors spend two full days on site, during which time the centre's activities should continue as normal. They can visit anywhere in the centre and carry out interviews with staff or even patients. Based on the self-evaluation reports and what they have seen, the audit group gives a first summary report about the accreditation, the designation, and points that can be improved. The chairman of the audit group is always a director of an OECI centre; two auditors are specialised in a relevant field of oncology, one is a quality manager and other personnel are from the OECI.

Peer review report

The peer review report is developed following some exchanges with the centre. The final report highlights the centre's strengths and the opportunities for improvement. When the report has been agreed on, a decision is made on accreditation and designation. If accreditation is given, it is valid for four years.

The cost for the full process of assessment and designation is €30,000 for a comprehensive cancer centre, which is paid to the OECI. The cost is lower for cancer centres and cancer units, at €25,000 and €20,000, respectively.

EurocanPlatform research programme

The EurocanPlatform programme is a research programme aimed at developing a designation system for excellent comprehensive cancer centres and comprehensive research centres, and outcome indicators for translational research. Proof of excellence includes recent research reports, grants awarded, and ongoing or completed research programmes and their outputs. The programme is also developing excellence indicators that will help us measure impact on patients.

The auditors. An OECI team visits the Instituto Portgués de Oncologia in Lisbon, as part of the accreditation procedure, March 2011

Summing up

We hope that the OECI accreditation programme and EurocanPlatform will help us to reduce fragmentation and increase harmonisation across cancer centres. The aim is for centres to work more closely together, with people visiting each other's centres and learning from each other in a network that supports competition and collaboration.

GM: *How do you accredit a paediatric oncology centre? Would a paediatric oncology centre have to be accredited as part of an adult oncology network or are you anticipating that there could be stand-alone paediatric oncology centres accredited in the future by OECI?*

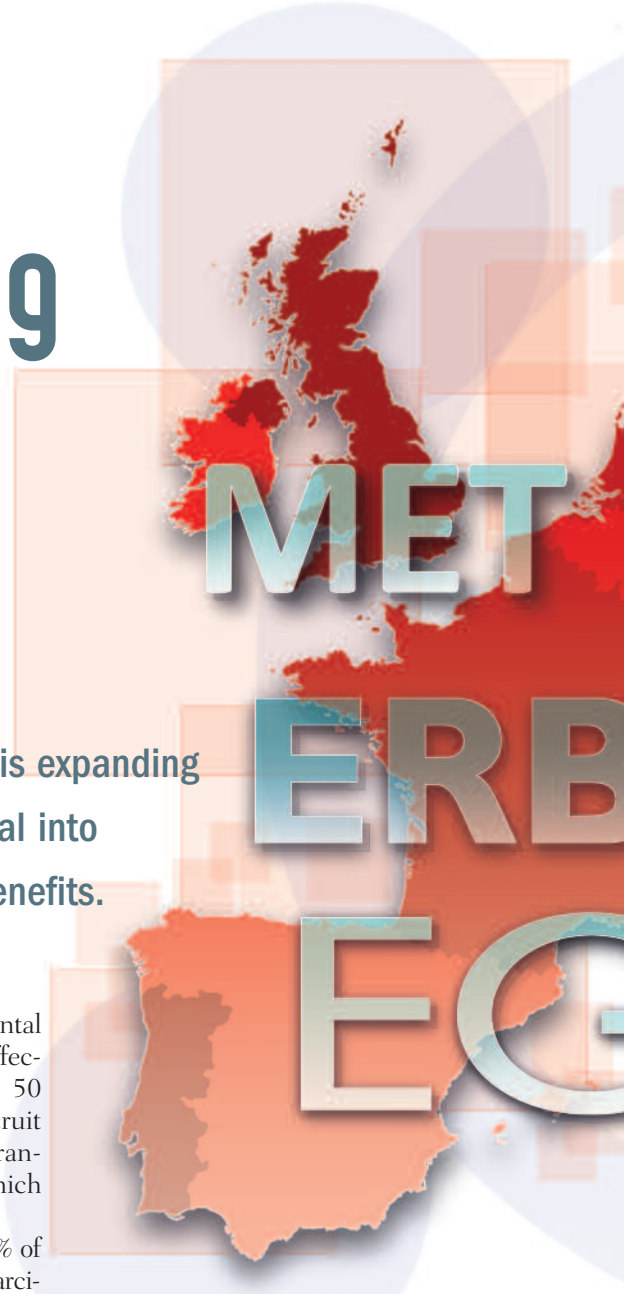
MS: *Paediatric oncology is facing the same issues as adult oncology. We are collaborating closely on this with a network of European paediatric oncology personnel. I think we could apply the accreditation model to paediatric units, but we might have to adapt some questions or add further standards related to paediatric care.*

GM: *What does a comprehensive cancer centre do for a patient in a district general hospital perhaps 100 kilometres from the centre?*

MS: *Comprehensive cancer centres are very important for other hospitals. Not all patients can be managed within the walls of the cancer centre. One of the very important standards is that centres must have networks, where they work with other professionals taking care of patients. It is the duty of the cancer centre to organise this network and the education of professionals within it.* ■

Lungscape: a living lung laboratory

PETER McINTYRE



The potential for personalising lung cancer therapies is expanding rapidly. The challenge now is how to turn that potential into reality as fast as possible so patients can reap the benefits.

A network of cancer centres is planning to transform the way that the findings of molecular research into non-small-cell lung cancer (NSCLC) are brought into clinical use. The 16 centres are pooling clinical data on 2400 lung cancer patients and sharing information on the genetic structure of tumour samples obtained during surgery.

The Lungscape project, part of the European Thoracic Oncology Platform, aims to harmonise standards and improve the quality of genetic testing in cancer centres, and increase understanding about which patients may benefit from the latest targeted therapies. Of the 16 centres, 14 are based in nine European countries, with one each in China and the USA.

Lungscape will eventually help oncologists select patients who stand to benefit from innovative or experimental treatments. The aim is to produce effective trials on subsets of maybe 50 patients, instead of having to recruit hundreds of patients into large randomised controlled trials from which most derive no benefit.

NSCLC accounts for about 85% of lung cancers and includes adenocarcinomas and squamous cell carcinomas. Survival rates are low unless the disease is caught early – which it isn't in the majority of cases. Patients are currently graded according to tumour size (T), the number of nodes affected (N) and the degree of metastasis (M). However, research is increasingly suggesting that this TNM categorisation is insufficient, and the focus now is on defining numerous small subgroups of lung cancer patients based on the increasing number of genetic alterations reported to be driving the disease. EGFR mutations are present in the tumour cells of about 15% of lung cancer patients with adenocarcinoma, and they may benefit from EGFR inhibitors. Trials have shown positive responses from treatment with Xalkori (crizotinib) for the 24% of NSCLC patients whose tumours show a gene fusion between EML4 and ALK. Up to 90% of these tumours showed a response in clinical trials, and in some

MAP: JASON COOK

cases there has still been no disease progression after 15 months.

In addition to these, genetic research is identifying many new mutations that need to be investigated in customised clinical trials that can be rapidly set up with small numbers of well-targeted patients. It is this that Rolf Stahel, president of the ETOP Foundation Council, hopes that Lungscape will help to deliver.

Lungscape centres keep control of the biopsy specimens taken from patients, which remain locally stored and analysed. Each patient's biological information, together with their clinical data, will be anonymised and shared in what they are calling the Lungscape iBiobank – a virtual biobank. During September 2012, Lungscape hit its target of enrolling 2400 patients.

ETOP's Rolf Stahel, who is a professor and medical oncologist at the University Hospital, Zurich, says Lungscape will describe the molecular landscape of non-small-cell lung cancer in Europe by testing the tissue samples with molecular markers and defining their characteristics. "We will get there by coordinating the work of 16 different sites, which will also allow us to establish a network for clinical trials where alterations that have been identified can be put into early-phase trials. We will know what proportion of patients will benefit and we will have established high-quality molecular testing. In addition, we will be able to determine whether certain molecular changes are associated with different prognostic outcomes independent of the anatomical staging."

As a first step, they will focus on patients found to have the ALK fusion gene and carry out a retrospective analysis to see whether the course of their disease and general outcome differed from those without the fusion.

Solange Peters, medical oncologist at the Lausanne Cancer Centre in

"Lungscape will describe the molecular landscape of non-small-cell lung cancer in Europe"

"Communication with all the centres and investigators is the key. You have to be on top of it every day"

Switzerland, is responsible for the content of and access to the virtual biobank. "These are all surgical patients who have undergone radical surgery for NSCLC stages I–III and we have all the basic demographics, tumour pathologic characteristics and patient clinical follow-up annotated for these patients. We will be able to identify in this subset of patients several parameters: outcome in terms of recurrence of the disease, outcomes in terms of general prognosis as well as the contribution related to other parameters. In about half of them we will also have data about recurrence."

It is unlikely that the patients will benefit directly from this first phase of Lungscape – aggregating and analysing anonymised data – although they may benefit from improved genetic testing by their own teams.

Peters says, "We have a philosophy of wanting to leave the tissue in every centre as, on the one hand people do not like to send their tissue material out, and on the other hand we want to empower all the centres with the capability to do all the testing in-house, with full quality assurance. We want all the tests to be done in-house and no tissue to travel. That is what makes it a virtual biobank."

More than two years have passed since Stahel and colleagues developed the ibiobank idea at a translational research meeting in Lugano in May 2010. Data collection began in April 2011, but it then took a further 18 months to complete the registration of all 16 centres and recruit the 2400 patients.

Difficult terrain

Money

There have been three main hurdles, the first being money. So far Lungscape has been supported entirely by the industry, with an unrestricted grant from Roche and financial sponsorship from Pfizer, which makes Xalkori, to test the samples for prevalence of ALK gene fusion, as well as support from Abbott Molecular. Xalkori has been approved for use by the US drug regulators, the FDA, for patients with advanced non-small-cell cancer who are ALK positive. In Europe, it has been recommended for conditional approval, with a final decision from the EMA pending. Stahel says they are now preparing an application for grant money from the EU. "We first needed to show what we can do, and we are proving that now, so I am quite optimistic that in the future we will be able to get other financial resources."

Local laws

The second task was to ensure that centres complied with their national legislation, had ethical approval and met all the logistical hurdles. ETOP is run from the coordinating centre in Bern, Switzerland, that coordinates the International Breast Cancer Study Group (IBCSG), and some key staff play the same role for both groups. Anita Hiltbrunner, director of the coordinating centre, explained how this had helped ETOP and Lungscape.

"We have a regulatory office who are very experienced from the IBCSG trials with all the needs and regulations in all the countries. We act as the point of contact for everything. We work very closely together by e-mail or teleconferences and we have regular meetings. Communication with all the centres and investigators is the key. It is something you have to be on top of every day."

The average time for a centre to be approved was about six months, but some took more than a year to reach agreement with their local or national ethics committees. The main issue was informed consent from patients. Although patients themselves do not need to undergo tests, the tumour material removed during their operation may in future undergo genetic tests that have not even been heard of today. Some of these tests may be carried out after a patient has died. While a surgeon in Zurich was able to get patients to sign a single form consenting to future research on this material, centres in other countries had to be more specific.

The UK turned out to be the most difficult country to convince; centres have to get both local and national approval. While two UK centres (the Royal Infirmary in Aberdeen and the Lung Cancer Group in Manchester) have joined the network, one other centre could not reach agreement. The Shanghai Chest Clinic in China is one of only two centres outside Europe to have been included; their national regulations make it clear that there can be no exceptions ever to the rule about tumour material not travelling.

Quality

The third hurdle was the quality of testing. Rosita Kammler, who coordinates translational research at IBCSG/ETOP, says that centres have to achieve the same high standards for immunohistochemistry and for the ALK-FISH (fluorescence *in situ* hybridisation) test, so that results are comparable.

"There are several steps involved to ensure that the end result is comparable from one site to the next. The first part is an internal validation. A pathologist constructed tissue microarrays (TMAs) from specific identified samples. These were sent to each centre with the TMA map to work up the staining. The next step is a blinded external quality assurance round. They receive blinded samples and send in results that are then reviewed."

Following the review, some centres were asked to undergo further practice and testing before approval. As new tests are developed they need to keep up to speed and Stahel says that they may get pathologists from each centre together to carry out training with a super specialist and then do another external evaluation. "One of the clear things in our minds was to raise quality standards and to empower all the participants to be very strong in this field."

The future shape of research

Lungscape has started to raise its profile, making presentations at the European Lung Cancer Conference in Geneva in April 2012 and oral and poster presentations at the ESMO meeting in Vienna in September/October 2012. Stahel says that the project is generating a real sense of excitement amongst the multidisciplinary teams that now lead the way in lung cancer diagnosis and treatment.

Genetic testing is becoming increasingly important to determine best treatment for non-small-cell lung cancer. The French National Cancer Institute (INCa) and French Government have been funding molecular testing for all lung cancer patients since 2011 and find that genetic testing can save money. Jean Charles Soria, professor of oncology at South Paris University, told the 3rd European Lung Cancer Congress, in April 2012, that the French government had invested €1.7 million in testing for the EGFR mutation and saved €65 million in treatment costs by identifying 15,000 patients who would not benefit from gefitinib (Iressa).

Other centres will join clinical trials that spin off from Lungscape. "The way to go to the future is a network of networks," says Stahel. "As well as our big European network, you would have sub-networks. In Switzerland, for example, Zurich and Basel are part of Lungscape, but the clinical trial could also include Lausanne, Geneva and Bern. It is networking of networks that will allow future research."

Peters says, "We have a kind of regrettable tradition for unselective patient trials which end up being not beneficial for the patient or are negative. Building this network is a way to develop procedures to build new trials designed for subsets of non-small-cell lung cancer patients and not a whole crowd. That way, new trials emerge from the knowledge, and not only the other way around."

ETOP is already planning phase 2 of Lungscape when it will switch from retrospective analysis to generating prospective trials of about 1000 patients who will be followed from the point of diagnosis. Although the central biobank will remain anonymised, each centre will use the genetic testing to determine treatment.

That is when it becomes really exciting, as Lungscape will follow long-term outcomes of patients who have received personalised treatment. Stahel said, "Two years from now we will have a lot of biomarker data with clinical correlations and we will have begun a prospective Lungscape. Five years from now we will have demonstrated which of the biomarkers adds to the diagnosis in addition to the anatomical staging." ■

CENTRES IN THE LUNGSCAPE NETWORK

There are currently 16 centres in the Lungscape network. The majority are in Europe, but the network also includes one specialist centre in the US and one in China, to widen the research base and to allow data to be compared inside and outside Europe.

University Hospital Leuven, Belgium
University Hospital Aarhus, Denmark
St James Hospital Dublin, Ireland
Ospedale Clinicizzato Chieti, Italy
Netherlands Cancer Institute Amsterdam, the Netherlands
Free University Medical Centre Amsterdam, the Netherlands
University Medical Centre Maastricht, the Netherlands
Medical University Gdansk, Poland
Vall d'Hebron University Hospital Barcelona, Spain
University Hospital Valencia, Spain
University Hospital Basel, Switzerland
University Hospital Zürich, Switzerland
Royal Infirmary Aberdeen, UK
Lung Cancer Group Manchester, UK
Shanghai Lung Cancer Centre, China
Roswell Park Cancer Institute, Buffalo, USA

"Five years from now we will have demonstrated which of the biomarkers adds to the diagnosis"

impactfactor

nature REVIEWS CLINICAL ONCOLOGY

Gastro-oesophageal cancer – is CROSSing over so hard to do?

MARIELA BLUM AND JAFFER AJANI

Suboptimal studies had established preoperative chemoradiation as the preferred strategy in the management of localised oesophageal cancer (LEC) and gastro-oesophageal cancer. The recent CROSS trial has now demonstrated considerable benefit from preoperative chemoradiation over surgery alone in patients with LEC. But are these results only reinforcing advocates of the preoperative chemoradiation strategy?

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The incidence of gastro-oesophageal adenocarcinoma has been rising for the past three decades, possibly owing to the dramatic increase in the BMI of adults in many societies, which has led to chronic gastro-oesophageal reflux disease and Barrett's oesophagus.[1–3] Squamous-cell carcinoma remains the most frequent histology in the endemic areas of the world, whereas adenocarcinoma is now the most common form of gastro-oesophageal cancer in the USA and parts of the Western World.[4] Historically, the management of localised oesophageal cancer (LEC) has been a source of intense debate. Complexities in the clinical decision-making for patients with LEC include the location of the primary tumour, histological subtype and tumour grade, clinical T and N stages, length of the tumour, ability of the patient to withstand surgery, and prevailing practice patterns. There may be unity in how to manage early-stage disease endoscopically (for example, stage Tis [carcinoma *in situ*] and T1a tumours), but opinion is divided in terms of how to manage thoracic T2–T3 tumours with any N stage or T1N+ tumours. In patients who can withstand surgery, thoracic LEC is best managed by multimodal therapy – preoperative chemotherapy or preoperative chemoradiation – because the five-year survival rates from primary surgery are dismal,[5] although high-volume centres have reduced surgical mortality considerably.[6] Multidisciplinary evaluation before starting any therapy is encouraged; however, it is not the norm in many countries (such as China and India, where most patients undergo surgery directly). In fact, preoperative chemotherapy for thoracic LEC is largely abandoned in North America but remains popular in many European countries.

Regarding the preoperative chemotherapy strategy, a North American randomised trial of this approach reported no benefit,[7] and a larger British trial from the Medical Research Council demonstrated only marginal benefit.[8] Preoperative chemoradiation, however, may be establishing itself as the strongest contender among all strategies.

Results from the CROSS trial[9] con-

ducted in Europe, have demonstrated considerable benefit from preoperative chemoradiation over surgery alone in selected patients with LEC. Yet the CROSS study may be reinforcing only the subscribers of the preoperative chemoradiation strategy and may not convert the proponents of preoperative chemotherapy or primary surgery. We feel that the report published by van Hagen et al.,[9] which represents the largest trial of its kind, may be transformative, although, we have our doubts about its impact on global approaches to LEC. Van Hagen et al.[9] randomly assigned 368 LEC patients with histologically confirmed squamous-cell carcinoma or adenocarcinoma (tumour stage T1N1 or T2–T3 with any N) to receive preoperative chemoradiation with paclitaxel and carboplatin in combination with 41.4 Gy of 3-D conformal radiation technique in 23 fractions given five days per week (n=180) or surgery alone (n=188). Although the tumours were well staged at baseline (even if no PET was carried out), patients were still selected according to age (18–75 years), weight loss (≤10%), and tumour not exceeding 8 cm in length or 5 cm in width. With a median follow up of 45.4 months, the median overall survival for the group receiving preoperative chemoradiation was 49.4 months versus 24 months for the surgery-only group (HR 0.67, 95%CI 0.495–0.871; P=0.003). The five-year overall survival rate was 47% versus 34%, favouring the chemoradiation group. This benefit was observed in both histological subgroups studied; however, the effect in the adenocarcinoma group (the largest cohort of the two histological subtypes: 275 patients vs 46) was marginal (P=0.049). Chemoradiation did not lead to excessive toxicity. Other benefits from preoperative chemoradiation included a higher rate of R0 resection and, as expected, a higher rate of pathological complete response in the surgical specimen. Data also supported the use of a moderate radiation dose of 41.4 Gy.

The CROSS trial is a well conceived and well-executed study that establishes level 1 evidence for preoperative chemoradiation for thoracic LEC and gastro-oesophageal cancers stage T1N1 or T2–T3 with any N stage. However, we are doubtful that these results will help establish a uniform global strategy for this group of LEC patients. This is in part because van Hagen et al.[9] are not optimistic about the preoperative chemoradiation strategy for patients with thoracic LEC and leave the door open to other options (even though the evidence of the benefit of other options is dubious). What will it take for us to have one global strategy for this group of patients with LEC? The answer to this quandary is unclear. However, those oncologists who prefer preoperative chemoradiation are on firm ground because of the CROSS trial results, and those who believe in surgery first or preoperative chemotherapy have little to base this on. We recommend preoperative chemoradiation as the preferred approach for the group of patients studied in the CROSS trial. We do not endorse surgery first or preoperative chemotherapy under normal clinical conditions, in which there is no contraindication to radiation. It is time to CROSS over.

> “Yet, the CROSS study may be reinforcing only the subscribers of preoperative chemoradiation”

Significant challenges remain when dealing with a difficult disease such as LEC. We must develop strategies that are appropriate for each histological subtype, for each anatomic location of LEC, and for each stage group of LEC. We must exploit the information provided by better imaging, such as PET. We must develop imaging methods that provide highly specific information – those that can image proliferation, apoptosis, hypoxia, receptor proteins, etc. before and after chemoradiation. Circulating tumour cells, mRNA, DNA, and miRNA can also increase our understanding of the aggressiveness of the cancer. We must carry out in-depth analyses of the molecular biology underlying oesophageal and gastro-oesophageal junction cancer and the genetic profile of the patients. We must focus more on methods to enable the immune system to recognise oesophageal and gastro-oesophageal cancer. Finally, we must identify patients who do not require oesophagectomy because their cancer is highly sensitive to chemoradiation.

We feel this can be achieved through establishing validated biomarker signatures and/or sophisticated imaging studies. We must, therefore, strive for oesophageal and gastro-oesophageal junction preservation and customisation of therapy. These are real challenges to deal with while we are debating our therapeutic preferences. These preferences are usually empiric in nature and help only a few patients, while we subject each one of our patients to the toxicity of preoperative therapy and significant life-altering consequences of oesophagectomy.[10] We would be remiss not to mention that we must also

Key point

The CROSS study, which provided excellent evidence in support of preoperative chemoradiation therapy of patients with localised gastro-oesophageal junction cancer, establishes a platform we can build on.

identify adults who are at high risk for developing oesophageal cancer, and detect and treat their cancers early. We may have the roadmap for making progress against LEC, but we seem to be walking in multiple directions. It is time to collaborate.

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Cetuximab dosing by rash – is the scaling of EVEREST meaningful?

SEBASTIAN STINTZING AND HEINZ-JOSEF LENZ

The small EVEREST trial has shown that the concept of guiding cetuximab dose escalation using the clinical parameter of acneiform skin rash is safe. However, as no significant increase of cetuximab efficacy could be observed, data from the ongoing EVEREST II trial must be awaited before dose escalation can be considered for clinical use.

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Skin toxicity in patients receiving cetuximab is positively associated with clinical outcome. The EVEREST study was conducted to examine the pharmacodynamics, pharmacokinetics, pharmacogenetics and safety of cetuximab dose escalation in a phase I/II setting in patients with metastatic colorectal cancer.[1] The study specifically investigated whether higher cetuximab doses would lead to a higher occurrence of grade 2 or 3 acneiform rash and superior treatment efficacy. In this study, 89 patients with or without minor (Common Terminology Criteria for Adverse Events [CTCAE] grade 0 or 1) acneiform skin rash after 21 days of receiving the standard dose of cetuximab (250 mg/m² per week after initial 400 mg/m²) were randomly assigned to receive either escalated cetuximab doses of up to 500mg/m² per week or to continue with standard dosing. Patients showing grade ≥2 skin toxicity (n=77) continued standard cetuximab dosing until progression and served as a control group. As with the BOND study,[2] patients were eligible to enrol after irinotecan failure and were administered irinotecan (180 mg/m² every other week) as the chemotherapeutic backbone. The published data of EVEREST[1] focus on the pharmacokinetic parameters, toxicity analyses and efficacy of the different treatment arms.

As expected, cetuximab serum concentrations rose under the influence of increased cetuximab administration. In terms of toxicity, there was no obvious difference in haematological adverse events between patients receiving the standard dose and those receiving the elevated regimen. Considering the non-haematological events associated with therapy, the proportion of patients developing hypomagnesaemia rose, and grade ≥2 cetuximab-related skin toxicities occurred at higher frequencies in the dose-escalated cohort, as predicted. In addition, the authors report efficacy data (objective response rate [ORR], progression-free survival and overall survival) with no significant differences between the different treatment groups. However, a trend towards higher ORR (30% vs 43%) and disease control rate (70% vs 83%) was seen in the dose-escalated group.

Acneiform skin toxicity is a class effect of all EGFR-targeting drugs currently in clinical use, including erlotinib for pancreatic and lung cancers and cetuximab and panitumumab for the treatment of metastatic colorectal and head-and-neck cancers.[2–4] Retrospective

analyses have shown a correlation between the grade of acneiform rash and the efficacy of anti-EGFR therapy – irrespective of the drug, underlying disease or whether the drug is given in combination with radiotherapy. For example, in colorectal cancer, the grade of acneiform rash is directly associated with the length of the observed survival.[5] In trials that investigated the efficacy of EGFR-targeting drugs in combination with chemotherapy, patients with colorectal cancer who did not experience any skin toxicity from the EGFR therapy had shorter survival periods than patients treated with chemotherapy alone. This correlation between rash and survival has been shown for erlotinib,[3] cetuximab and panitumumab.[4,5] However, the trials each showed an overall survival benefit for EGFR-targeting agents with chemotherapy over the chemotherapy alone arms, irrespective of skin rash. These benefits were significant for erlotinib in pancreatic cancer (P=0.03; HR 0.81)[3] and had a trend to significance in cetuximab (P=0.48; HR 0.91)[4] and panitumumab (P=0.072; HR 0.83).[5] Several host-related factors have been proposed to be predictive of the development of acneiform rash. Aside from the fact that younger male patients (<65 years) are more likely to develop acneiform rash,[3] molecular factors such as the single-sequence CA repeat intron-1 polymorphism of the EGFR also predict the likelihood of acneiform rash.

Acneiform rash is attributed to the direct inhibition of EGFR expressed in undifferentiated proliferating keratinocytes in the basal and suprabasal layers of the epidermis and outer layers of the hair follicle. This inhibition leads to premature keratinocyte differentiation and increased cell–cell attachment as well as reduced growth and migration, which collectively disrupt the formation of a normal, protective epidermal barrier. Indeed, Fracasso and colleagues revealed that elevated serum concentrations of cetuximab in patients receiving escalated cetuximab doses (with a maximum serum level reached at doses of 400 mg/m² per week) were accompanied by reduced EGFR protein expression in the skin compared with patients receiving the standard dose.[6] This decrease was already evident at a cetuximab dose of 250 mg/m² per week and there was a trend to even lower levels of EGFR expression in the 400 mg/m² cohort.[6] A separate study that focused on saturation of the EGFR with cetuximab in patients with head-and-neck tumours who were treated with cetuximab showed that EGFR saturation within the tumour was dose dependent; an initial cetuximab loading dose of 400 mg/m² followed by 250 mg/m² weekly achieved almost complete saturation of EGFR in the tumour tissue.[7] These data suggest that the acneiform rash reflects the saturation of EGFR in the tumour. Furthermore, the study demonstrated that a small number of patients might benefit from 400 mg/m² per week cetuximab in terms of downregulating EGFR in the skin – resulting in acneiform rash – and maximising EGFR saturation by cetuximab in the tumour.

> "...there was no obvious difference in haematological adverse events between patients receiving the standard dose and those receiving the elevated regimen"

An inflammatory response – including increased production of cytokines such granulocyte-macrophage colony-stimulating factor and recruitment of inflammatory cells – also contributes to the development of the characteristic rash.[8] This inflammatory response suggests that EGFR inhibition increases the recruitment of inflammatory cells involved in the immune response against the tumour. Such an immune reaction might further explain the correlation between the occurrence of acneiform rash and a superior outcome, which is observed irrespective of KRAS mutational status.[4] Although a correlation between acneiform grade and the inflammatory response inside the tumour in the presence of cetuximab therapy has not been shown, Tabernero and colleagues have demonstrated that downregulation of proteins downstream of EGFR – such as phosphorylated EGFR and phosphorylated MAPK – and upregulation of STAT3 (signal transducer and activator of transcription 3 protein) in the skin do occur in tumours treated with cetuximab in a dose-dependent manner.[9]

The efficacy of anti-EGFR drugs is also influenced by the presence of genetic alterations, which inhibit downstream pathway signalling. In colorectal cancer, in addition to KRAS codon 12 and 13 mutations, NRAS, BRAF (V600E), PI3KCA and AKT1 (E17K) mutations as well as expression of PTEN are associated with resistance to cetuximab. Furthermore, EGFR mutations and KRAS amplification were also noted to be associated with cetuximab resistance.[10] If the mechanism by which tumours are resistant to cetuximab therapy was inherited, dose escalation would not likely show benefit. However, patients without the genetic mutations that confer inherited resistance, and

Key point

Higher doses of cetuximab are well tolerated and lead to increased grade ≥2 acneiform rashes; we await the results from the prospective EVEREST II trial, which will test whether patients with increased acneiform rash have longer overall survival.

whose tumours do not show complete EGFR saturation when receiving standard doses of cetuximab, might benefit from escalated cetuximab doses. Those higher doses might further downregulate EGFR expression in the skin and, therefore, the patients might develop a higher grade of acneiform rash.

As almost 90% of patients treated with cetuximab display some grade of acneiform rash, the therapeutic window of cetuximab dose escalation might be narrow. Although the small size of the EVEREST trial limits the conclusions we can draw, these preliminary data warrant further studies. We await the data of the prospective EVEREST II trial before we can consider the clinical implications of the concept of escalating cetuximab guided by the clinical parameter of acneiform rash.

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Competing interests

Sebastian Stintzing declares associations with Amgen, Merck KGaA and Roche. Heinz-Josef Lenz declares an association with Merck KGaA. See the original article online for full details of the relationships.

newsround

Selected reports edited by Janet Fricker

Glioblastoma: temozolomide offers alternative to radiotherapy in elderly patients

■ The Lancet

Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options for elderly patients with glioblastoma, a phase III study from the Nordic Clinical Brain Tumour Study Group (NCBTSG) has found.

In 2004 chemoradiotherapy with temozolomide became the standard of care for patients with glioblastoma, but its introduction was based on a pivotal study in which patients were aged 70 years or younger. In other studies, increasing age has been shown to be a negative prognostic factor, leading to the suggestion that elderly and frail patients might not be viewed as candidates for combined therapy.

To define an evidence-based treatment for patients aged 60 years or older with glioblastoma, NCBTSG investigators undertook a randomised trial to compare health-related quality of life and safety in patients randomised to single-agent temozolomide chemotherapy, short-course hypofractionated radiotherapy (34.0 Gy administered in 3.4 Gy fractions over two weeks) or standard six-week radiotherapy (60.0 Gy administered in 20.0 Gy fractions over six weeks). Both patients and staff were aware of treatment assignments.

Between February 2000 and June 2009, 342 patients with newly diagnosed, histologically confirmed glioblastoma (WHO grade IV astrocytoma) from 28 centres in Austria, Denmark, France, Norway, Sweden, Switzerland and Turkey were recruited.

In the study, 291 patients were randomised across three treatment groups: temozolomide (n=93), hypofractionated radiotherapy (n=98), and standard radiotherapy (n=100). An additional 51 patients were randomised across only two groups: temozolomide (n=26) and hypofractionated radiotherapy (n=25).

Results for the three-group randomisation show that median overall survival was 6.0 months for standard radiotherapy versus 8.3 months with temozolomide (HR 0.70, 95%CI 0.52–0.93, P=0.01); and 7.5 months with hypofractionated radiotherapy (HR 0.85, 95%CI 0.64–1.12, P=0.24).

In the two-group randomisation, overall survival was 8.4 months for patients who received temozolomide versus 7.4 months for patients who received hypofractionated radiotherapy (HR 0.82, 95%CI 0.63–1.06; P=0.12).

For patients older than 70 years, survival was better with temozolomide (HR 0.35; P<0.001) and with hypofractionated radiotherapy (HR 0.59; P=0.02), in comparison with standard radiotherapy.

An additional finding was that patients treated with temozolomide who had tumour MGMT promoter methylation showed significantly longer survival than those without (HR 0.56; P=0.02).

As expected, the most common grade 3–4 adverse events in the temozolomide group were neutropenia (n=12) and thrombocytopenia (n=18).

"We found that temozolomide chemotherapy is a potential alternative to radiotherapy in elderly and frail patients," write the authors. The results, they add, support the predictive value of MGMT promoter methylation as a useful biomarker in guiding treatment decisions around temozolomide.

In an accompanying commentary, Phioanh Leia Nghiemphu and Timothy Cloughesy, from the University of California at Los Angeles, write, "The Nordic study is a well balanced randomised trial that provides provocative results and greatly contributes to the understanding of geriatric neuro-oncology. For patients aged 70 years and younger, radiation at least did not negatively affect survival and provides insight into a molecular subgroup that might be well suited to treatment with temozolomide."

A collective effort towards systematic prioritisation of the effects of all factors on prognosis, they add, will enable classification of prognostic subgroups for prospective investigation and eventually lead to definition of relevant optimum treatments.

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■ P Nghiemphu, T Cloughesy. Glioblastoma therapy in the elderly: one age does not fit all. *ibid*, pp 857–858

R-CHOP best for older patients with mantle-cell lymphoma

■ New England Journal of Medicine

For older patients with mantle-cell lymphoma, a rituximab-based chemotherapy regimen followed by rituximab maintenance therapy improves survival, according to the results of a study by the European Mantle Cell Lymphoma Network.

Treatment options for older patients with mantle-cell lymphoma are limited, as the standard first-line therapy approach of high-dose cytarabine, followed by autologous stem-cell transplantation, is usually not feasible. The median age at diagnosis for mantle-cell lymphoma is about 65 years.

In the current study, Habbeje Kluin-Nelemans and colleagues, from the Groningen University Medical Centre, in the Netherlands, compared two induction regimens, followed by two different maintenance therapies for those showing a response.

Between January 2004 and October 2010 investigators randomly assigned 560 patients aged 60 years or older with mantle-cell lymphoma, stage II to IV, who were not eligible for high doses to one of two alternative treatment arms: six cycles of rituximab, fludarabine and cyclophosphamide (R-FC) every 28 days or eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 21 days. Altogether 532 of these patients were included in the intention-to-treat analysis and 485 in the primary analysis.

Results showed that the four-year survival rate was 47% for R-FC versus 62% for R-CHOP (*P*=0.005). Furthermore, 10% of patients in the R-FC group died during the first remission versus 4% in the R-CHOP group.

Complete remission rates were 40% for R-FC versus 34% for R-CHOP (*P*=0.10), and progressive disease was 14% for R-FC versus 5% for R-CHOP.

Among those re-randomised to maintenance therapy, 58% of those receiving rituximab were in remission after four years versus 29% receiving interferon-alpha (HR for progression or death 0.55, 95%CI 0.36–0.87, *P*=0.01). Furthermore, among patients who had a response to R-CHOP, the four-year survival of patients receiving maintenance therapy with rituximab was 87%, versus 63% for interferon-alpha (*P*=0.005).

"In conclusion, older patients with mantle-cell lymphoma who have a response to R-CHOP and continue to receive rituximab as maintenance therapy have a longer life expectancy than those who receive maintenance therapy with interferon-alfa," write the authors.

The outcomes for R-FC, they add, were disappointing, given the high expectations that this regimen had in the early 2000s. In future, they add, it might be "attractive" to combine rituximab-based maintenance regimens with other drugs shown to be active against mantle-cell lymphoma, such as bendamustine or molecularly targeted approaches.

"However, physicians need to be aware of the potential interactions between the initial therapy and the maintenance regimen," write the authors.

■ H Kluin-Nelemans, E Hoster, O Hermine et al. Treatment of older patients with mantle cell lymphoma. *NEJM* 9 August 2012, 367:520–531

Observation effective in prostate cancer with low PSA

■ New England Journal of Medicine

For men with localised prostate cancer detected through prostate-specific antigen (PSA) testing, radical prostatectomy delivers no survival benefits over 12 years follow-up in comparison to observation alone, the PIVOT study has reported. Subgroup analyses of the US study, however, suggest surgery reduces mortality among prostate cancer patients with high PSA levels.

Although the lifetime risk of receiving a diagnosis of prostate cancer is about 17%, the risk of dying from the disease is approximately 3%, suggesting conservative management may be appropriate for some men. But the observation option is rarely offered due to lack of evidence from randomised trials.

In the Prostate Cancer Intervention versus Observation Trial (PIVOT) study, Tim Wilt, from the University of Minnesota School of Medicine, Minneapolis, and colleagues conducted a randomised trial to compare radical prostatectomy with observation in men who had received a diagnosis of clinically localised prostate cancer in the early era of PSA testing. Between November 1994 and January 2004, 731 men with localised prostate cancer were randomised to radical prostatectomy (*n*=364) or observation (*n*=367). Patients, who had a mean age of 67 years, were recruited from 44 Department of Veterans Affairs sites and eight National Cancer Institute sites and followed through until January 2010.

Results during a median follow-up of 10 years show 47.0% of men assigned to radical prostatectomy died compared with 49.9% assigned to observation (HR 0.88, 95%CI 0.71–1.08; *P*=0.22). Additionally, 5.8% of men assigned to radical prostatectomy died from prostate cancer or treatment compared with 8.4% assigned to observation (HR 0.63, 95%CI 0.36–1.09; *P*=0.09). During the first 30 days after surgery, perioperative complications occurred in 21.4% of men undergoing radical prostatectomy, with the most common complication being wound infections (4.3%).

Among men with a PSA value greater than 10 ng/ml, surgery reduced all-cause mortality by 13.2%. Among men with intermediate-risk tumours (determined by a PSA value of 10.1–20.0 ng/ml, a Gleason score of 7, or a stage T2b tumour), those randomly assigned to surgery had a 31% relative reduction in all-cause mortality compared with those assigned to observation.

"Our findings support observation for men with localized prostate cancer, especially those who have a low PSA value and those who have low-risk disease," write the authors. The study, they add, was conducted in the early era of PSA testing. "The current practices of performing repeated PSA testing, using a lower PSA

threshold for biopsy, obtaining more tissue-biopsy cores, and performing a repeat biopsy after initially negative findings increase the detection of smaller volume indolent cancers. ...These factors increase the likelihood of over diagnosis and overtreatment."

In an accompanying commentary, Ian Thompson from the University of Texas Health Science Center, San Antonio, and Catherine Tangen from the Fred Hutchinson Cancer Center, Seattle, stress that the men most likely to benefit from therapy are those whose prostate cancers pose the greatest risk of death from cancer. "The screening, detection, and treatment we provide must focus on cancers that matter, and future clinical trials must do so as well," they write.

■ T Wilt, M Brawer, K Jones. Radical prostatectomy versus observation for localised prostate cancer. *NEJM* 19 July 2012, 367:203–213

■ I Thompson, C Tangen. Prostate cancer – uncertainty and a way forward. *ibid* pp 270–271

Pyridoxine not recommended in hand-foot syndrome

■ **British Journal of Cancer**

While pyridoxine (vitamin B6) may reduce the incidence of severe hand-foot syndrome (HFS) and the need for capecitabine dose modifications in patients with advanced colorectal or breast cancers, no antitumour benefits were detected, the CAP-IT study has reported. Routine use of pyridoxine for HFS, conclude the UK investigators, should not be recommended.

Pyridoxine is frequently used to treat capecitabine-induced HFS. Since HFS resembles the rat disease acrodynia, known to be caused by pyridoxine deficiency, treatment with pyridoxine has been proposed. There is, however, no evidence for benefit. In the current study, Pippa Corrie and colleagues from Addenbrooke's Hospital, Cambridge, performed a randomised placebo-controlled trial to determine whether pyridoxine avoided the need for capecitabine dose modifications and furthermore improved outcomes.

Altogether 106 patients with a median age of 73 years scheduled for palliative single-agent capecitabine (65% of whom had colorectal cancer and 35% breast cancer) were randomised in a 1:1 ratio, between December 2004 and June 2009, to receive either concomitant pyridoxine (50 mg; *n*=53) or matching placebo (*n*=53) three times daily, commencing on the day capecitabine chemotherapy was initiated. Treatment continued until disease progression, toxicity or patient preference. After discontinuation, patients were followed up for 12 weeks.

Results showed that 37% of patients randomised to pyridoxine avoided capecitabine dose modifications versus 23% randomised to placebo (RR 0.59, 95%CI 0.29–1.20; *P*=0.15). Furthermore, 9% of patients in the pyridoxine group experienced grade 3/4 HFS-related adverse events versus 17% in the placebo group (*P*=0.26). There was a trend towards pyridoxine decreasing progression-free survival (PFS), with a median PFS duration of 7.4 months for pyridoxine and 9.9 months for placebo (HR 1.62, 95%CI 0.91–2.88; *P*=0.095).

"Pyridoxine appeared to reduce the incidence of grade 3/4 HFS and the need for capecitabine dose modifications, although this did not translate into an improvement in outcome from chemotherapy itself; the trend towards poorer PFS in the pyridoxine arm was not statistically significant," write the authors. "Whether pyridoxine might in fact negatively influence chemotherapy efficacy is intriguing, although not conclusive," they add.

The authors also refer to an earlier study, which reported significantly lower tumour responses to capecitabine at the higher pyridoxine dose level, while a second study, involving use of pyridoxine in advanced ovarian cancer, found it reduced durations of response to treatment with hexamethylamine plus cisplatin.

■ P Corrie, R Bulusu, C Wilson, et al. A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *Br J Cancer* 7 August 2012, 107:585–587

Study suggests new standard of care for platelet transfusions

■ **The Lancet**

Therapeutic platelet transfusions could become the new standard of care for patients with haematological malignancies who have received autologous stem cell transplantation, a German study suggests. Prophylactic platelet transfusion, however, should remain the standard for patients with acute myeloid leukaemia for whom special attention is needed due to increased risk of central nervous system (CNS) bleeding.

Routine prophylactic platelet transfusion is the standard of care for patients with severe thrombocytopenia with morning platelet counts of $10x10^9$ per litre or lower. However, whether such transfusions are necessary for clinically stable patients with no bleeding has long been debated. Small studies performed 30 years ago showed favourable results for the therapeutic strategy (where transfusions are offered following bleeds), but these results are no longer considered applicable to current clinical practice due to changes in chemotherapy dose intensities and supportive care.

In 2005 and 2006 two single-centre pilot studies showed that a new strategy of therapeutic platelet transfusion was feasible, with no increased risk in major bleeding and a substantially reduced number of platelet transfusions compared with historical controls. In the current study, the same team, led by Hannes Wandt from the Klinikum Nuremberg Nord, Germany, investigated whether these results could be reproduced prospectively in a multicentre randomised study.

In the study, patients aged 16–80 years undergoing intensive chemotherapy for acute myeloid leukaemia or autologous haematopoietic stem-cell transplantation for haematological cancers were randomised to receive platelet transfusions either when bleeding occurred (therapeutic strategy, *n*=199) or when morning platelet counts were $10x10^9$ per litre or lower

(prophylactic strategy, *n*=197). Altogether 190 of the patients had acute myeloid leukaemia and 201 had undergone autologous transplantation.

The study was undertaken between February 2005 and May 2010 at eight haematology centres in Germany.

Results show that, for all patients, the primary endpoint of platelet transfusions occurred in 2.44% of patients in the prophylactic group versus 1.63% in the therapeutic group (*P*<0.0001). For those with acute myeloid leukaemia, transfusions occurred in 2.68% randomised to the prophylactic group versus 1.83% to the therapeutic group, representing a 31.6% reduction (*P*<0.0001). While for those who had autologous transplantation, transfusions occurred in 1.8% in the prophylactic group versus 1.18% in the therapeutic group, representing a 34.2% reduction (*P*=0.0193).

For patients undergoing autologous transplantation, randomisation to the therapeutic arm did not increase the risk of major haemorrhage; but for those with acute myeloid leukaemia in the therapeutic arm, the risk of non-fatal grade 4 bleeding significantly increased (mostly CNS) compared to the prophylactic group (*P*=0.0095).

"Our findings show that the number of platelet transfusions was significantly lower, by roughly a third, in the therapeutic group than in the prophylactic group. However, this clinically meaningful difference must be weighed against the increased bleeding risk," write the authors.

The new strategy of therapeutic platelet transfusions in patients who have received autologous stem cell transplantation, they add, should be used only by haematology centres where staff are experienced in the approach and can react in a timely way to first signs of CNS bleeding.

In an accompanying commentary, Neil Blumberg and colleagues from the University of Rochester Medical Center, New York, write, "The emerging hypothesis, ... is that transfused platelets might be promoters of arterial and venous thrombosis, tumour growth, and metastasis. These possibilities provide additional reasons to favour a restrictive policy for platelet transfusion in view of the moderate benefits of transfusion shown in autologous transplant patients."

■ H Wandt, K Schaefer-Eckart, K Wendelin et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet*, published online 7 August 2012, doi:10.1016/S0140-6736(12)60689-8

■ N Blumberg, J Heal, G Phillips, et al. Platelets – to transfuse or not to transfuse. *ibid*, doi:10.1016/S0140-6736(12)60983-0

Survival advantage for centralisation of vulvar surgery

■ European Journal of Cancer

Centralisation of care for women with vulvar squamous cell carcinoma (SCC) is associated with improved survival, a Dutch study has reported.

In 2000, guidelines from the Dutch Society of Obstetrics and Gynaecology recommended centralisation of care for patients with vulvar SCC. Benefits identified for this approach included the development of expertise, and the opportunity to give patients appropriate treatment from experienced clinicians using new techniques that might improve prognosis and/or lower treatment-related morbidity. The strategy was also thought to facilitate training and research.

The cornerstone of treatment for vulvar carcinoma is surgery, which offers an excellent chance of cure. In other rare malignancies, such as oesophageal and pancreatic carcinomas, associations have been found between the volume and/or specialisation of a hospital on the one hand and better survival on the other hand. In recent years, treatment of patients with early-stage vulvar SCC has shifted from inguinofemoral lymphadenectomy to the sentinel lymph node dissection (SLND) procedure. To meet quality standards, it has been suggested that surgeons should perform SLND surgery at least 510 times per year. For a rare tumour such as vulvar SCC, with an annual incidence of one to two cases per 100,000 women, this would require centralisation.

In the current study, Loes van den Einden and colleagues, from Radboud University, Nijmegen Medical Centre, in the Netherlands, set out to determine whether guidelines had been adopted and whether such adoption had resulted in improvements in survival. The guidelines were introduced in 2000. For the study, data on all patients diagnosed with vulvar malignancies between 1989 and 2008 in the eastern part of the Netherlands were retrieved from the population-based cancer registry held by the Comprehensive Cancer Centre IKNL. Data for patients diagnosed before the introduction of guidelines (1989–1999) were compared with those for patients diagnosed after (2000–2008).

A total of 382 patients with vulvar SCC with invasion >1 mm, who had an indication for groin surgery, were included in the analysis. In the first decade, 62% (123 out of 198 patients) were treated in a specialised oncology centre, which increased to 93% (172 out of 184 patients) in the more recent period (*P*<0.0001). The five-year relative survival was 69% for the first period, compared to 75% for the second period. After adjustment for age and stage, being treated in a specialised oncology centre was found to be an independent prognostic factor for survival. Patients treated in a specialised oncology centre in the period 2000–2008 appeared to have comparable five-year relative survival rates compared to patients treated in specialised centres in the period 1989–1999.

"In conclusion, the present study showed that centralisation of the treatment of patients with vulvar SCC who need groin surgery has been well adopted in the Eastern part of the Netherlands. Being treated in a specialised oncology centre is associated with a better survival," write the authors.

■ L van den Einden, K Aben, L Massuger et al. Successful centralisation of patients with vulvar carcinoma: a population-based study in the Netherlands. *Eur J Cancer*, September 2012, 48:1997–2003

My World

Maria João Cardoso is head breast surgeon at the Champalimaud Cancer Centre in Lisbon. She founded the patient support centre Mama Help, and leads a research group at the Institute for Systems and Computer Engineering, in Porto, on improving outcomes in breast reconstruction.

Why I chose to work in cancer

Because it was and still is a mysterious disease with so many things yet to discover. Working in an institution dedicated to translational research, and being a part of the process, makes your career much more interesting.

What I love most about my job

Patients' gratitude! When a patient looks at you as the one who pushed death away, it has a profound effect on you.

The hardest thing about my job

When disease progresses and we have to tell patients the bad news. In those moments you feel your patient's despair as if it were your own. But you have to move on and learn to deal with that feeling.

What I've learnt about myself

That patients are my best teachers. They are usually strong and optimistic and even when they are facing a difficult situation, they manage to see the best side of it. I've learnt from their examples and found ways to use what I've learnt.

I'll never forget...

The opening of our first support centre for breast cancer patients in 2011, called Mama Help. It was a project in my head for almost 10 years. Being able to transform it into reality, and watching the benefit it brings to patients... simply marvellous!

A high point in my career

The invitation by Dra. Fátima Cardoso, director of the Breast Unit, to be the head breast surgeon at the Champalimaud Cancer Centre. I felt very important and honoured. To be able to work with one of the best specialists in breast cancer in the world was a dream come true.

I wish I were better at...

Being more tolerant with others. When you work hard you tend to evaluate others by your own parameters and it can often be difficult to accept even minor failures. I feel that younger doctors are sometimes really afraid of me – I can see it in their faces!

What I value most in a colleague

Honesty. When you work in a team, your input, as well as others', is important to achieve the best results. Intellectual and scientific honesty are fundamental ingredients.

The most significant advance in my specialty in recent years

Immediate breast reconstruction and sentinel node biopsy. Quality of life is very important, particularly with prolonged survival. These procedures offer patients two major improvements in their quality of life.

My advice to someone entering my specialty today would be...

Be a hard worker. You will not achieve anything without hard work. When you love this work you never stop. You finish your appointments when your patients want you to, not when you finish your daily agenda! And after 12 hours of surgery and an absolutely impossible week you still spend your weekend correcting articles or rushing to meet research deadlines.

What I wish I'd learnt at medical school

Health economics. When you start working, you have no idea about health costs. We have learnt to act as others before us did. Private and public medicine has enormous costs and oncology is one of its major consumers. To serve patients better we need to have at least some idea of how much it will cost to treat them. ■